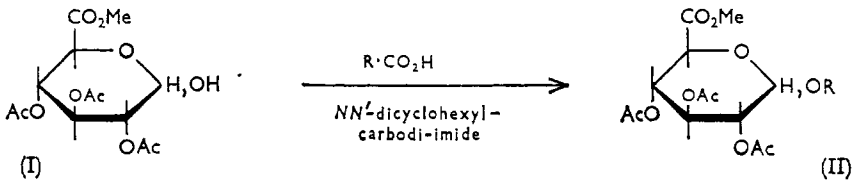
883. *Glucuronic Esters. Part I. Synthesis of Methyl 2,3,4-Tri-O-acetyl-1-O-acyl-D-glucopyranuronates by Use of Carbodi-imide.**

By N. Pravdić and D. Keglević.

An attempt has been made to prepare 1-*O*-acyl derivatives of glucuronic acid, especially those of the indole series, by the carbodi-imide method. The hemiacetal hydroxyl group of methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate (I) was easily esterified with various aliphatic, aromatic, and indole acids, yielding methyl 2,3,4-tri-*O*-acetyl-1-*O*-acyl-D-glucopyranuronates (II) (Table 1). The reaction was catalysed by pyridine and carried out



either with equimolar amounts of the reactants (A), or in the case of strong acids with an excess of carbodi-imide (B) and (C). In most cases a mixture of anomers was formed; only with 1-*O*-cinnamoyl derivative were the pure α- and β-anomers readily separated. However, some acids bearing bulky groups yielded only the (—)-isomer. The 1-*O*-benzoyl and 1-*O*-*p*-methoxybenzoyl derivatives showed optical rotations identical with those of the pure β-anomers isolated from biological material.[1,2] Thus, it appears that the formation of α-ester bonds with bulky aglycones is sterically hindered. The separation of anomers by fractional crystallisation was inefficient. The infrared spectra of the products showed a sharp band (890—898 cm.$^{-1}$) characteristic of the β-glucopyranose series.[3] Only with the α-1-*O*-cinnamoyl derivative was this peak absent. In no case could a discrete absorption for α-anomers (844 ± 8 cm.$^{-1}$) [3] be detected.

In order to obtain starting material of known configuration, methyl 2,3,4-tri-*O*-acetyl-1-*O*-benzyl-β-D-glucopyranuronate [4] and its α-anomer were debenzylated. The rate of cleavage differed considerably, and mixtures of anomers were obtained in both cases.

The effect of pyridine on the formation of (II) was studied (Table 3). In pyridine-catalysed reactions mutarotation of (I) always preceded esterification. Without pyridine, products enriched in the β-form were obtained; *i.e.*, the equatorial hydroxyl group of (I) is more reactive than the axial one.

Experimental.—Specific rotations were measured at 20—23° (*c* 1 ± 2% in $CHCl_3$) unless stated otherwise. Infrared spectra were recorded for Nujol mulls on a Perkin-Elmer model 137 instrument.

Methyl 2,3,4-tri-O-acetyl-D-glucopyranuronate (I). To methyl 2,3,4-tri-*O*-acetyl-1-bromo-α-D-glucopyranuronate [5] (8 g.) in anhydrous acetone (50 ml.), water (0·36 ml.) and silver carbonate (6 g.) were added at room temperature. The mixture was shaken for 12 hr., the precipitate was filtered off and washed with warm acetone, and the combined filtrate and washings were concentrated to a syrup which solidified on standing. The process was speeded up by seeding, and gave the ester (I) (6·6 g., 98%), m. p. 91—92°, $[\alpha]_D$ +96°, +72° (*c* 1 in H_2O)

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[1] Goebel, *J. Biol. Chem.*, 1937—1938, **122**, 649.
[2] Sammons and Williams, *Biochem. J.*, 1946, **40**, 223.
[3] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[4] Helferich and Berger, *Chem. Ber.*, 1957, **90**, 2492.
[5] Bowering and Timell, *J. Amer. Chem. Soc.*, 1960, **82**, 2827.

{lit.,[6] m. p. 113° $[\alpha]_D^{20}$ +72° (*c* 1 in $CHCl_3$), +75° (*c* 1 in H_2O)} (Found: C, 46·7; H, 5·5; OAc, 39·0. Calc. for $C_{13}H_{18}O_{10}$: C, 46·7; H, 5·4; OAc, 38·6%); $\nu_{max.}$ 3450 (sharp, OH), 1760 (acetate C : O), and 890 cm.$^{-1}$ (assigned to β-anomer). The ester slowly mutarotated in chloroform to a constant value of +82° after 7 days. On addition of a trace of either hydrobromic acid (28% in glacial acetic acid) or dry pyridine to a fresh solution the value changed to a constant one of +81° in ~20 min.

Methyl 2,3,4-*tri*-O-*acetyl*-1-O-*acyl*-D-*glucopyranuronates* (II). (A) *Standard procedure.* A solution of the acid (2 mmoles) in dichloromethane (5—10 ml.) was added gradually to a solution of the ester (I) (2 mmoles), *NN'*-dicyclohexylcarbodi-imide (2 mmoles), and dry pyridine (0·2 ml.) in dichloromethane (2 ml.) and set aside at room temperature for 4—15 hr. The dicyclohexylurea was filtered off and the solvent evaporated to dryness. When the yield of dicyclohexylurea was less than 70% of the theoretical amount, the residue was treated with anhydrous ether (5 ml.) and a second crop of dicyclohexylurea was removed immediately. The ethereal filtrate was evaporated and the oily residue dried over sulphuric acid until solidification took place. Generally, analytically pure products were obtained after one or two recrystallisations. The pure β-anomer of the 1-*O*-cinnamoyl derivative separated after the first crystallisation; from the mother-liquor the α-anomer crystallised on standing.

(B) *Modified procedure.* The molar ratio of *NN'*-dicyclohexylcarbodi-imide to acid was 1·2 : 1. The treatment with absolute ether precipitated the corresponding *N*-acyl-*NN'*-dicyclohexylurea, which was filtered off. The ethereal filtrate was treated as in (A).

(C) *Anhydride procedure.* To a solution of the acid (6 mmoles) in dichloromethane (15—25 ml.), dry pyridine (0·3 ml.) and *NN'*-dicyclohexylcarbodi-imide (3 mmoles) were added. The mixture was left to stand for 4 hr. and dicyclohexylurea was filtered off. To the filtrate containing the acid anhydride, a second portion of *NN'*-dicyclohexylcarbodi-imide (3 mmoles) and the ester (I) (3 mmoles) were added. The mixture was then treated as in (B).

TABLE 1.

Methyl 2,3,4-tri-*O*-acetyl-1-*O*-acyl-D-glucopyranuronates (II).

						Found (%)			Reqd. (%)	
R	Method	Yield (%)	Solvent [a]	M. p. or b. p./μ	$[\alpha]_D$	C	H	Formula	C	H
Acetyl	A	71	a	146—155°	+45°	48·1	5·3	$C_{15}H_{20}O_{11}$	47·9	5·4
Propionyl	A	82	b	102—124	+55	49·1	5·6	$C_{16}H_{22}O_{11}$	49·2	5·7
Butyryl	A	76	b	85—86	+63	50·3	5·9	$C_{17}H_{24}O_{11}$	50·5	6·0
n-Decanoyl	A	68		165—175/15	+57	56·8	7·2	$C_{23}H_{36}O_{11}$	56·6	7·4
Phenylacetyl	A	81	a	99—101	+25	55·8	5·5	$C_{21}H_{24}O_{11}$	55·8	5·4
Diphenylacetyl	A	26	c	171—172	−43	61·2	5·3	$C_{27}H_{28}O_{11}$	61·4	5·3
Diethylacetyl	A	57		150—180/16	+67	52·5	6·4	$C_{19}H_{28}O_{11}$	52·8	6·5
2-Phenylbutyryl	A	67	a	102—116	+35	57·4	6·0	$C_{23}H_{28}O_{11}$	57·5	5·9
Benzoyl	C	55	c	142—143	−16	54·5	5·1	$C_{20}H_{22}O_{11}$	54·8	5·1
m-Nitrobenzoyl	C	93	a	119—120	+37	49·9	4·4 [b]	$C_{20}H_{21}NO_{13}$	49·7	4·4
p-Methoxybenzoyl	A	27	a	147—149	−24	54·0	4·9	$C_{21}H_{24}O_{12}$	53·9	5·2
Cinnamoyl-β-	A	31	c	170—171 [c]	−15	57·2	5·5	$C_{22}H_{24}O_{11}$	56·9	5·2
-α-		37		114—115 [d]	+131	57·2	5·4			
Tri-*O*-acetylgalloyl	A	66	a	170—172	+8	51·2	4·7	$C_{26}H_{28}O_{17}$	51·0	4·6
Indol-3-ylacetyl [e]	B	31	d	104—108	−19	56·3	5·3 [b]	$C_{23}H_{25}NO_{11}$	56·2	5·1
5-Benzyloxyindol-2-ylcarbonyl	B	56	a	178—179	−29	59·7	4·9 [f]	$C_{29}H_{29}NO_{12}$	59·7	5·0
5-Benzyloxyindol-3-ylacetyl [g]	A	47	a	152—153	−32	60·3	5·2 [h]	$C_{30}H_{31}NO_{12}$	60·3	5·2

[a] a, ethanol; b, propan-2-ol; c, methanol; d, ether–light petroleum. [b] Found: N, 3·0; requires N, 2·9%. [c] Needles. [d] Flakes. [e] R_F 0·96 in methanol–benzene–butan-1-ol–water (4 : 2 : 2 : 2) (blue spot with Erlich's reagent). [f] Found: N, 2·5; requires N, 2·4%. [g] R_F 0·92 (same solvent system). [h] Found: N, 2·6; requires N, 2·4%.

The 1-*O*-acyl derivatives prepared are summarised in Table 1 and the *N*-acyl-*NN'*-dicyclohexylureas in Table 2. The effect of pyridine on the preparation of the 1-*O*-propionyl derivative is shown in Table 3.

Methyl 2,3,4-*tri*-O-*acetyl*-1-O-*benzyl*-β-D-*glucopyranuronate*. Methyl 2,3,4-tri-*O*-acetyl-1-bromo-α-D-glucopyranuronate (7·5 g.), benzyl alcohol (4 g.), and silver carbonate (10·5 g.)

[6] Ishidate and Nakajima, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 433.

TABLE 2.

N-Acyl-*NN'*-dicyclohexylureas.

N-Acyl group	Yield [a] (%)	M. p.[b]	Found (%) C	H	N	Formula	Required (%) C	H	N
Benzoyl	16	161—162° [c]							
m-Nitrobenzoyl	35	174—175	64·5	7·5	11·5	$C_{20}H_{27}N_3O_4$	64·3	7·3	11·3
Indol-3-ylacetyl	10	175—176	72·4	7·9	11·3	$C_{23}H_{31}N_3O_2$	72·4	8·2	11·0
5-Benzyloxyindol-2-ylcarbonyl	21	188—189	73·7	7·5	8·5	$C_{29}H_{35}N_3O_3$	73·5	7·5	8·9

[a] Based on the acid used. [b] From ethanol. [c] Zetzsche and Fredrich, *Ber.*, 1939, **72***B*, 1735, give m. p. 160—161°.

TABLE 3.

Effect of pyridine on the preparation of methyl 2,3,4-tri-*O*-acetyl-1-*O*-propionyl-D-glucopyranuronate.

Method	$[\alpha]_D$ of (I)	Yield (%)	M. p.	$[\alpha]_D$	Found (%) C	H	Calc. for $C_{16}H_{22}O_{11}$ C	H
A	+96°	87	102—124°	+55°	49·1	5·6		
A [a]	+96	59	102—131	+41	49·1	5·6		
C [b]	+96	85	107—122	+61	49·4	5·7	49·2	5·7
— [c]	+96	86	104—127	+62	49·1	5·8		
A	+72 [d]	66	102—126	+54	49·6	5·7		
A [a]	+72 [d]	36	149—151	+9	49·6	5·7		

[a] Without pyridine. [b] No precipitation of the *N*-acyl-*NN'*-dicyclohexylurea occurred on treatment of the oily residue with ether. [c] Dry pyridine (0·1 ml.) and propionic anhydride (0·13 g., 1 mmole) were added to a solution of the ester (I) (0·334 g., 1 mmole) in dichloromethane (2 ml.), left overnight, and worked up as in (A). [d] Starting material prepared by catalytic debenzylation of the β-benzyl compound.

in dry benzene (50 ml.) were shaken at room temperature for 12 hr. Evaporation of the filtrate gave the β-ester (3 g., 38%), m. p. 133—134° (from methanol), $[\alpha]_D$ −67° {lit.,[4] m. p. 135—136°, $[\alpha]_D^{18}$ −66·2° (in $CHCl_3$), from a preparation using $Hg(CN)_2$}.

Methyl 2,3,4-*tri*-O-*acetyl*-1-O-*benzyl*-α-D-*glucopyranuronate*. A solution of the above β-ester (1·53 g.) and titanium tetrachloride (0·6 ml.) in dry chloroform (50 ml.) was refluxed for 75 min. After cooling, the mixture was washed with sodium hydrogen carbonate and water, dried, and evaporated to a syrup which gave the α-*anomer* (0·94 g., 62%), m. p. 72—73° (from 50% aqueous ethanol), $[\alpha]_D$ +146° (Found: C, 56·5; H, 5·5. $C_{20}H_{24}O_{10}$ requires C, 56·6; H, 5·7%).

Reductive cleavage of the benzyl derivatives (II; R = CH_2Ph). The hydrogenations were carried out on a 1 mmole scale in chloroform (15 ml.) at room temperature. After removal of the catalyst the filtrate was evaporated and the residual oil worked up. Debenzylation of the β-anomer over 10% palladised barium sulphate (0·3 g.) was complete after 16 hr. and the product (I) isolated as a colourless foam (0·327 g., 98%), $[\alpha]_D$ +72° (Found: C, 46·7; H, 5·7. Calc. for $C_{13}H_{18}O_{10}$: C, 46·7; H, 5·4%), $\nu_{max.}$ 3450, 1750, and 892 cm.$^{-1}$. On addition of a trace of pyridine mutarotation to a constant value of +82° occurred in 20 min. Reduction of the α-anomer over 10% palladised barium sulphate (1 g.) was incomplete after 5 days, but gave the ester (I) (0·18 g., 55%), m. p. 89—92°, $[\alpha]_D$ +82° (Found: C, 46·7; H, 5·2%), $\nu_{max.}$ 3450, 1750, and 890 cm.$^{-1}$. Addition of a trace of pyridine caused no change in the optical rotation.

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TRACER LABORATORY, INSTITUTE "RUDER BOŠKOVIĆ,"
ZAGREB, YUGOSLAVIA.

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884. 7,7-*Dimethylnorcarane and* 3-*Methoxy*-7,7-*dimethylnorcarane.*

By E. D. Andrews and W. E. Harvey.

Compounds containing the norcarane ring system may be readily prepared by the Simmons–Smith reaction,[1] but this procedure and others involving addition to the double bond of cyclohexene or substituted cyclohexenes cannot be readily modified to yield 7,7-dialkylnorcaranes. The compounds named in the title were prepared by the thermal decomposition, in the presence of a small amount of potassium hydroxide,[2] of the indazoles formed from hydrazine and 2-isopropylidenecyclohexanone or its 4-methoxy-derivative.* This procedure, which has been employed for the synthesis of carane [3] and car-2-ene,[4] gave good yields of the norcaranes with only small amounts of olefins, and isolation of the intermediate indazoles appeared to be unnecessary.

Nuclear magnetic resonance measurements confirmed the structure of the indazole and of dimethylnorcarane. The former showed a resonance at 5·70 τ, which disappeared when the sample was treated with deuterium oxide, and is therefore assigned to a proton attached to nitrogen. The spectrum of 7,7-dimethylnorcarane showed a peak at 9·03 τ equivalent to two methyl groups, and a doublet at *ca.* 9·45 τ attributable to the two bridgehead protons.

Experimental.—Analyses are by Dr. A. D. Campbell, University of Otago.

Ethyl 2,2-ethylenedioxy-5-methoxycyclohexanecarboxylate. Ethyl 5-methoxy-2-oxocyclohexanecarboxylate [5] (20 g.), 1,2-ethanediol (12 g.) and toluene-*p*-sulphonic acid (0·5 g.) in benzene (75 ml.) were heated in a flask fitted with a Dean–Stark separator until separation of water was complete. The benzene solution was washed with water, sodium carbonate solution, and water, and concentrated, giving the *spiro-ester* (20·5 g., 84%), b. p. 103°/0·3 mm., n_D^{25} 1·4660 (Found: C, 59·0; H, 8·5. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·25%).

2-Isopropylidene-4-methoxycyclohexanone. The above spiro-compound (20 g., 1 mol.) in ether (75 ml.) was added with stirring and cooling to methylmagnesium iodide (2·6 mol.) in ether (50 ml.). The resulting suspension was heated under reflux with stirring for 3 hr. then poured on to ice and ammonium chloride. The ethereal solution was separated, washed with water, dried, and concentrated, and the product in methanol (100 ml.) and water (50 ml.) was treated with concentrated hydrochloric acid (1·5 ml.) at 80° for 2 hr. The solution was neutralised with sodium carbonate and most of the methanol was removed under reduced pressure. Isolation with ether gave the *ketone* (10 g., 73%), b. p. 75—76°/0·4 mm., n_D^{25} 1·4910, $\lambda_{max.}$ 252·5 mμ (log ε 3·8), $\nu_{max.}$ (liquid) 1687 cm.$^{-1}$ (conjugated C=O) (Found: C, 70·8; H, 9·7. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). It gave a single peak on gas chromatography on a column of Apiezon L on Celite at 150°. The *2,4-dinitrophenylhydrazone* crystallised from alcohol as red plates, m. p. 120—121° (Found: C, 55·2; H, 5·2. $C_{16}H_{20}N_4O_5$ requires C, 55·2; H, 5·8%).

3,3a,4,5,6,7-Hexahydro-3,3-dimethyl-2H-indazole. 2-Isopropylidenecyclohexanone [6] (27·3 g.) was added to hydrazine hydrate (99%; 20 g.) with stirring and cooling so that the temperature did not exceed 50°. The solution was cooled, diluted with ether, washed three times with water, dried (Na_2SO_4), and concentrated. Distillation gave the *indazole* (22·5 g., 75%), b. p. 114°/13 mm., n_D^{25} 1·5307, $\lambda_{max.}$ 230 mμ (log ε 2·35), $\nu_{max.}$ (liquid) 3300 (N–H), 1635 cm.$^{-1}$ (C=N) (Found: C, 71·2; H, 10·7; N, 18·6. $C_9H_{16}N_2$ requires C, 71·0; H, 10·6; N, 18·4%). The *N-benzoyl derivative* had m. p. 120—121° (from aqueous ethanol) (Found: C, 75·2; H, 7·9; N, 10·6. $C_{16}H_{20}N_2O$ requires C, 75·0; H, 7·9; N, 10·9%).

7,7-Dimethylnorcarane. (*a*) The above indazole (11·2 g.) and powdered potassium hydroxide (0·5 g.) were heated under reflux at 220—240° until the vigorous evolution of gas ceased. The

* Since this work was completed Closs and Böll [*J. Amer. Chem. Soc.*, **1963**, **85**, 3904 (footnote)] have stated that 7,7-dimethylnorcarane can be prepared by this method.

[1] Simmons and Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 5323; 1959, **81**, 4256.
[2] Beech, Turnbull, and Wilson, *J.*, 1952, 4686.
[3] Kishner and Zavodovsky, *J. Russ. Phys. Chem. Soc.*, 1911, **43**, 1132.
[4] Naves and Papazian, *Helv. Chim. Acta*, 1942, **25**, 984.
[5] Cook and Lawrence, *J.*, 1938, 58.
[6] Mukherji, Gandhi, and Vig, *J. Indian Chem. Soc.*, 1956, **33**, 853.

product, in ether, was washed with dilute sulphuric acid, water until neutral, 1% potassium permanganate solution, and water, then dried (Na_2SO_4), and concentrated, giving 7,7-*dimethylnorcarane* (6·4 g., 70%), b. p. 153—156°, n_D^{25} 1·4547 (Found: C, 86·8; H, 13·3. C_9H_{16} requires C, 87·0; H, 13·0%). It gave a single peak on gas chromatography (10% Apiezon L on Celite, 100°) and had $\nu_{max.}$ (liquid) 3000s, 2940s, 2880s, 1455s, 1380s, 1235m, 1140m, 980s, 849m, 775s cm.$^{-1}$.

(*b*) 2-Isopropylidenecyclohexanone (10 g.) in absolute ethanol (25 ml.) was added dropwise with stirring to hydrazine hydrate (3·6 g.) in absolute ethanol (10 ml.) at 0°. The solution was heated under reflux for 2 hr., then concentrated under reduced pressure. Treatment with potassium hydroxide and working up as before gave 7,7-dimethylnorcarane (7·0 g., 78%).

3-*Methoxy*-7,7-*dimethylnorcarane*. 2-Isopropylidene-4-methoxycyclohexanone (6·6 g.) and hydrazine hydrate (2·0 g.), treated as above, gave 3-*methoxy*-7,7-*dimethylnorcarane* (4·35 g., 72%), b. p. 205—210°/105 mm., n_D^{25} 1·4618 (Found: C, 77·3; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%), which gave a single peak on gas chromatography.

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VICTORIA UNIVERSITY OF WELLINGTON,
WELLINGTON, NEW ZEALAND.

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885. *Tetrahydropyrene as a Source of 2-Pyrenyl Derivatives.*

By ROGER BOLTON.

DIRECT attack of the pyrene nucleus by electrophilic reagents usually introduces substituents to the 1-position only.[1,2] The synthesis of 2-pyrenyl derivatives from pyrene is a tedious process of several stages and poor yields.[1] Bavin synthesised 4-nitropyrene by the nitration of 1,2,3,6,7,8-hexahydropyrene and dehydrogenation of the product;[3] similar treatment of 4,5,9,10-tetrahydropyrene gives 2-nitro-4,5,9,10-tetrahydropyrene, m. p. 110·8—111·6°, which can be dehydrogenated to 2-nitropyrene by the action of iodine in nitrobenzene. The position of substitution was proven by reduction of the nitro-compound to 2-aminopyrene, and the preparation of the *N*-acetyl derivative.[1]

Reduction of 2-nitro-4,5,9,10-tetrahydropyrene gave the amine, m. p. 168·6—169·6°. These two compounds have been described as the nitration product of [2,2]metacyclophane and its derived amine; although they were shown to be derivatives of 4,5,9,10-tetrahydropyrene, the position of substitution was not rigidly proven.[4] 2-Chloro-4,5,9,10-tetrahydropyrene could be prepared from the amine by the Sandmeyer reaction; dehydrogenation of this compound yielded 2-chloropyrene, identical with the product of a similar reaction with 2-aminopyrene.

The Friedel–Crafts reaction upon 4,5,9,10-tetrahydropyrene gave 2-acetylpyrene after dehydrogenation; owing to the presence of some pyrene and dihydropyrene in the starting material, some 1-isomer was also produced, the removal of which considerably lowered the yield of pure product. In the preparations of 2-benzoylpyrene, the intermediate 2-benzoyl-4,5,9,10-tetrahydropyrene was isolated in 84% yield; the subsequent dehydrogenation gave 2-benzoylpyrene in 80% yield.

Experimental.—2-*Nitro*-4,5,9,10-*tetrahydropyrene*. Tetrahydropyrene (6·0 g., 0·03 mole) in acetic anhydride (250 ml.) was treated with nitric acid (*d* 1·42; 1·8 ml.), by Bavin's method.[3] Chromatography of the product on alumina in light petroleum (b. p. 60—80°) gave the pure

[1] Vollmann, Becker, Corell, and Streeck, *Annalen*, 1937, **531**, 1.
[2] Bavin, Ph.D. Thesis, London, 1952.
[3] Bavin, *Canad. J. Chem.*, 1959, **37**, 1614.
[4] Allinger, da Rooge, and Hermann, *J. Amer. Chem. Soc.*, 1961, **83**, 1974.

nitro-compound (3·94 g., 52%), m. p. 110·8—111·6° (from ethanol) (lit.,[4] 110—111°) (Found: C, 76·65; H, 5·25; N, 5·7. Calc. for $C_{16}H_{13}NO_2$: C, 76·5; H, 5·2; N, 5·55%) after a small fore-run of unchanged hydrocarbon.

2-*Amino*-4,5,9,10-*tetrahydropyrene*. Reduction of 2-nitro-4,5,9,10-tetrahydropyrene (672 mg., 0·00267 mole) with hydrazine hydrate (100%; 5 ml.) and 5% palladised charcoal catalyst in ethanol (50 ml.),[5] gave the amine (99%), m. p. 168·8—169·6° (from ethanol) (lit.,[4] 165—166·5°).

2-*Chloro*-4,5,9,10-*tetrahydropyrene*. Reaction of cuprous chloride (600 mg.) in hydrochloric acid (12N; 25 ml.) upon the diazonium salt solution from 2-amino-4,5,9,10-tetrahydropyrene (585 mg., 0·00264 mole) in hydrochloric acid (6N; 25 ml.) gave the *chloro-compound* (311 mg., 49%), needles, m. p. 125·2—125·6° [from light petroleum (b. p. 60—80°)] (Found: C, 79·9; H, 5·45; Cl, 14·75. $C_{16}H_{13}Cl$ requires C, 79·83; H, 5·44; Cl, 14·73%). Heating this compound with the theoretical amount of sulphur at 250° for 1 hr. gave crude 2-chloropyrene, m. p. 123—133°, which was purified by isolation of its 2,4,7-trinitrofluorenone complex and decomposition of this upon alumina. Crystallisation from light petroleum (b. p. 60—80°) gave pure *2-chloropyrene*, m. p. 143·5—145·0°. The same product was obtained (48%), m. p. 146·8—147·0°, by carrying out the Sandmeyer reaction with 2-aminopyrene (Found: C, 80·95; H, 3·75. $C_{16}H_9Cl$ requires C, 81·2; H, 3·85%).

2-*Nitropyrene*. This could not be successfully separated from chloranil when Bavin's conditions for dehydrogenating 1,2,3,6,7,8-hexahydro-4-nitropyrene were applied to 2-nitro-4,5,9,10-tetrahydropyrene.[3] When 2-nitro-4,5,9,10-tetrahyropyrene (983 mg., 0·00391 mole) was boiled in nitrobenzene (50 ml.) with iodine (2047 mg., 0·00806 mole) for 6 hr., there was no obvious evolution of hydrogen iodide or any diminution in the colour of the solution, but, after removal of the excess of iodine and the solvent, chromatography upon alumina in benzene–light petroleum (1 : 1) gave *2-nitropyrene* (560 mg., 58%), m. p. 201—202·5° (from benzene) (Found: C, 77·95; H, 3·8; N, 5·7. $C_{16}H_9NO_2$ requires C, 77·7; H, 3·65; N, 5·65%). The reduction of this with hydrazine hydrate and palladised charcoal in benzene–ethanol (1 : 1) gave 2-aminopyrene, m. p. 215—216° (lit.,[1] 207°), which was identified as its *N*-acetyl derivative, m. p. 234—235° (lit.,[1] 229°), and by its ultraviolet spectrum.[6] Further confirmation was obtained by isolating small amounts of 2-hydroxypyrene, m. p. 211—212° (lit.,[1] 207°), from the diazonium reaction of 2-aminopyrene with cuprous chloride.

2-*Benzoyl*-4,5,9,10-*tetrahydropyrene*. Aluminium chloride (4·0 g.) was slowly added to a solution of tetrahydropyrene (6·0 g., 0·03 mole) and benzoyl chloride (3·5 ml., 0·031 mole) in carbon disulphide (100 ml.). Hydrolysis and crystallisation from ethanol gave the *ketone* (7·7 g., 84%), m. p. 123·5—125·0° (Found: C, 89·0; H, 5·8. $C_{23}H_{18}O$ requires C, 89·0; H, 5·85%). Heating this compound with the theoretical amount of sulphur at 240° for 1 hr. gave a melt which completely solidified on cooling. The product was dissolved in boiling methylene chloride, poured into five volumes of hot ethanol, and cooled, giving *2-benzoylpyrene* (6·0 g., 80%), m. p. 182—183° (Found: C, 89·9; H, 4·6. $C_{23}H_{14}O$ requires C, 90·15; H, 4·6%).

2-*Acetylpyrene*. This was prepared in the same way, using acetyl chloride (2·1 g., 0·031 mole), and the crude ketone (100%) was dehydrogenated directly by heating with sulphur. Crystallisation of the crude product (5.30 g., 70%) from ethanol gave the pure *ketone*, m. p. 141—142° (Found: C, 88·0; H, 5·05. $C_{18}H_{12}O$ requires C, 88·5; H, 4·95%). Oxidation of the crude ketone with sodium hypochlorite gave an acid which, after extensive purification, had m. p. 270—274°, and which seemed to be pyrene-1-carboxylic acid (lit.,[1] 274°) although its solution in sulphuric acid showed only a weak fluorescence.[1] However, both m. p. and mixed m. p. with 1-acetylpyrene (m. p. 90—91°) showed that our acetylpyrene was not the 1-isomer. The pyrene-1-carboxylic acid may have arisen from the presence of pyrene (5%) and dihydropyrene (5%) in the tetrahydropyrene used, since it was obtained in yields of less than 1%.

The author thanks Dr. A. Bernhardt for microanalyses and Professor P. B. D. de la Mare for his interest in this work and for helpful suggestions.

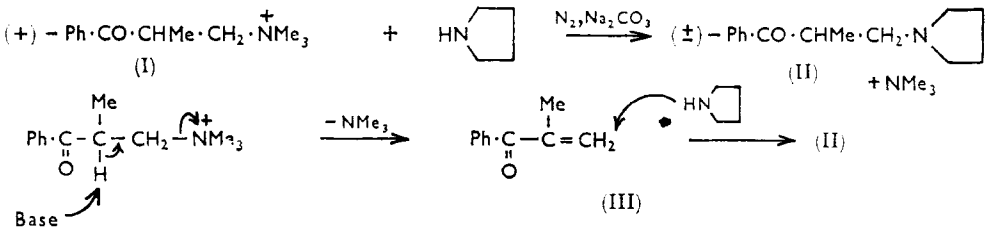
CHEMISTRY DEPARTMENT, BEDFORD COLLEGE, LONDON N.W.1. [*Received, January 25th,* 1964.]

[5] Bavin, *Canad. J. Chem.*, 1958, **36**, 238.
[6] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.

886. *Mechanism of a Mannich Base Exchange Reaction.*

By A. F. Casy and J. L. Myers.

During the course of configurational studies in propoxybenzene * and related compounds,[1] evidence for the mechanism of a Mannich base exchange reaction was obtained. When optically active 3-dimethylamino-2-methyl-1-phenylpropan-1-one methiodide (I) was treated with pyrrolidine and sodium carbonate, the product of exchange (II) proved to be racemic. The dextrorotatory Mannich base (I) in dimethylformamide suffered only a small loss in optical activity when shaken with sodium carbonate in a sealed tube (to prevent loss of trimethylamine) and in the absence of pyrrolidine. These results suggest the main cause of racemisation to be implication of the asymmetric centre in the exchange process, rather than simple enolisation, and support the generally accepted, but unestablished, two-



stage mechanism [2] (shown here) for alkylations involving Mannich bases. Further evidence for this pathway was provided by the isolation of isopropenyl phenyl ketone (III) when the reaction was carried out in an open vessel with omission of exchanging base. The ketone (III) gave a Mannich ketone in high yield when mixed with dimethylamine or pyrrolidine in dimethylformamide. Although the conversion of Mannich bases and their quaternary salts into αβ-unsaturated ketones is well known [*e.g.*, Burckhalter and Fuson [3] obtained the ketone (III) by steam-distillation of 3-dimethylamino-2-methyl-1-phenylpropan-1-one hydrochloride] the significance of the present experiment lies in proof of the formation of an αβ-unsaturated ketone under conditions similar to those employed in the alkylation.

Experimental.—(+)-3-Dimethylamino-2-methyl-1-phenylpropan-1-one hydrochloride, m. p. 161—162°, $[\alpha]_D^{20}$ +48° (*c* 1·0 in EtOH) {lit.,[4] m. p. 153—155°, $[\alpha]_D^{25}$ +47° (*c* 1·0 in H_2O)} was obtained by resolution of the racemic base with (−)-dibenzoyltartaric acid. The base derived from the (+)-hydrochloride gave a *methiodide*, m. p. 158—159° (from acetone), $[\alpha]_D^{15}$ +34·0° (*c* 1·0 in EtOH), $[\alpha]_D^{15}$ +35·5° (*c* 0·9 in EtOH containing 6·3% dimethylformamide) (Found: C, 46·15; H, 5·8%; Equiv., 334. $C_{13}H_{20}INO$ requires C, 46·85; H, 6·0%; Equiv., 333).

Exchange reaction. Nitrogen was bubbled through a solution of the (+)-methiodide (I) (5·0 g., 0·015 mole) and pyrrolidine (1·17 g., 0·017 mole) in dimethylformamide (30 ml.) containing sodium carbonate (0·8 g., 0·0075 mole) in suspension. After 2 hr. the mixture was diluted with water (100 ml.) and extracted with ether. The dried extract was evaporated and the residue treated with ethanolic hydrochloric acid and crystallised from ether–methanol to give (±)-*2-methyl-1-phenyl-3-(1-pyrrolidinyl)propan-1-one hydrochloride*, m. p. 149·5° (Found: C, 65·4; H, 7·9; N, 5·7%; Equiv., 258. $C_{14}H_{20}ClNO$ requires C, 66·3; H, 7·9; N, 5·5%; Equiv., 254). A 5% solution in water was optically inactive. A mixture of the (+)-methiodide (I) (222 mg.), sodium carbonate (35·5 mg.), and dimethylformamide (1·33 ml.) was shaken in a sealed tube for 2 hr., diluted with ethanol, filtered, and the filtrate adjusted to 20 ml. with ethanol. After

* G.M.C. approved name for 4-dimethylamino-3-methyl-1,2-diphenyl-2-propionyloxybutane.

[1] Casey and Meyers, *J. Pharm. Pharmacol.*, 1964, **16**, 455.
[2] Hellman and Opitz, "Alpha-aminoalkylierung," Verlag Chemie, G.m.b.H., Weinheim/Bergstr., 1960, p. 12.
[3] Burckhalter and Fuson, *J. Amer. Chem. Soc.*, 1948, **70**, 4184.
[4] Pohland, Peters, and Sullivan, *J. Org. Chem.*, 1963, **28**, 2483.

this treatment and in this solvent mixture the (+)-methiodide had $[\alpha]_D^{15}$ +30·5°. Nitrogen was passed for 2 hr. through a mixture of the (±)-methiodide (I) (20 g.), sodium carbonate (3·2 g.), and dimethylformamide (120 ml.) at 60—70°. The product was diluted with water and extracted with ether; the dried extract was evaporated and the residue (12 g.) distilled to give isopropenyl phenyl ketone (10 g.), b. p. 71—73°/1·0 mm., $\lambda_{max.}$ (EtOH) 246 mμ (ε 9900) (Found: C, 82·3; H, 6·75. Calc. for $C_{10}H_{10}O$: C, 82·2; H, 6·85%). It gave a pyrazoline with phenylhydrazine, m. p. 120—121·5° (from ethanol) (lit.,[3] 119—121°). A mixture of the ketone (III) (5·0 g.), pyrrolidine (5·0 g.), sodium carbonate (2·5 g.), and dimethylformamide (15 ml.) was left overnight at room temperature and processed as before. The residual oil, freed from the excess of pyrrolidine by being heated on a steam-bath under reduced pressure, was treated with ethanolic hydrochloric acid and crystallised from ethyl acetate–methanol to give the Mannich base (II) hydrochloride (2·5 g.), m. p. and mixed m. p. 150—152°.

Equiv. wts. were determined by titration with 0·02N-perchloric acid in glacial acetic acid with Oracet Blue B as indicator.

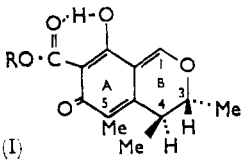
SCHOOL OF PHARMACY, CHELSEA COLLEGE OF SCIENCE AND TECHNOLOGY,
MANRESA ROAD, LONDON S.W.3. [*Received, January 24th*, 1964.]

887. *The Chemistry of Fungi. Part XLIV.*[1] *The Conformation of Citrinin.*

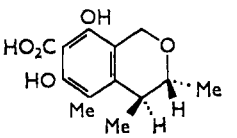
By D. W. MATHIESON and W. B. WHALLEY.

THE nuclear magnetic resonance spectrum of the fungal metabolite, citrinin [2] (I; R = H) has been measured in deuteriochloroform at 60 mc./sec. and assignments made as in the Table.

(I; R = H)	τ	*H*	*J*	Assignments
Two doublets with centre line of each superimposed	8·75	3	6·5	CH_3 at C-4 coupled geminally to H
	8·62	3	6·5	CH_3 at C-3 ,, ,, ,,
Single peak	7·97	3	—	CH_3 at C-5
Quartet centred at	6·96	1	6·5	H at C-4 coupled geminally to CH_3
Quartet centred at	5·16	1	6·5	H at C-3 ,, ,, ,,
Single peak at	1·7	1	—	H at C-1
Single peak at	−3·7	1	—	H of OH at C-8 and H of carboxyl group } signals disappear on deuteration
Single peak at	−5·2	1	—	



(I)



(II)

The signals from the methyl residues at C-3 and C-4 appear as a triplet because the line on the down-field side of the C-4 methyl doublet coincides with the up-field component of the C-3 methyl doublet. In the methyl ester (I; R = Me) the two doublets are clearly resolved and appear at τ 8·77 (C-4 methyl; *J*, 6 c./sec.) and 8·56 (C-3 methyl; *J*, 6 c./sec.). The negative τ value of the hydroxyl signal is due to strong intramolecular hydrogen bonding. The diamagnetic shift to τ 0·18 of this signal in the methyl ester indicates a reduction of this interaction.

The protons at positions 3 and 4 are coupled to the methyl groups on the same carbon atoms and exhibit two quartets. The absence of further (vicinal) splitting allows the conformation of citrinin, in which the C-3 and C-4 methyl groups are *trans* to each other,[1] to be defined. In contrast to ring A, ring B is relatively mobile, about positions 2, 3, and 4.

[1] Part XLIII, Bell, Chatterjea, Holker, Staunton, and Whalley, *J.*, 1964, 4307.
[2] Johnson, Robertson, and Whalley, *J.*, 1950, 2971.

Hence two conformations are possible, namely, (*a*) in which the dihedral angle θ between the protons is ≃60°, with the C-3 and C-4 methyl groups quasi-axial, and (*b*) in which θ is ≃180° and the methyl residues are quasi-equatorial.

The vicinal coupling constant for θ ≃ 180° is about 10—11 c./sec., and would probably lead to further splitting of the quartets concerned, whilst for θ ≃ 60° the coupling constant is 1—2 c./sec.[3] Subsidiary splitting of this order was observed in the spectra of the methyl ester (I; R = Me) and in dihydrocitrinin (II): we conclude that citrinin has the conformation (*a*). This accords with general principles since in (*b*) the methyl groups at C-3, C-4, and C-5 are nearly coplanar and subject to a greater degree of steric hindrance than in conformation (*a*)

The spectra were measured on a Varian A.60 spectrometer by Miss J. Lovenack. We thank the Wellcome Trust for financial assistance.

THE SCHOOL OF PHARMACY, THE UNIVERSITY, LONDON. [*Received, March 4th*, 1964.]

[3] Conroy, in "Advances in Organic Chemistry," Interscience, New York, 1960, Vol. 2, p. 310.

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888. *Rate Factors for the Detritiation of the* 1- *and* 2-*Positions of Biphenylene.*

By J. M. BLATCHLY and R. TAYLOR.

THE appearance of a preliminary communication by Streitweiser and Schwager on the hydrogen exchange of biphenylene [1] prompts us to describe our own results for this reaction. While these authors established only the tritiation rates of the 1- and the 2-positions, relative to one another, we have determined the detritiation rates relative to a single position in benzene, which means that they can be compared with partial rate factors measured for a large number of other aromatic compounds under similar conditions,[2] *viz.* in anhydrous trifluoroacetic acid at 70·1°.

The rate factors are 14,100 for the 2-position and 104 for the 1-position. The 2-position is therefore much more reactive than a corresponding 4-position in biphenyl ($f^{4\text{-Ph}} = 163$),[3] but less reactive than a corresponding 2-position in fluorene ($f^{2\text{-Fl}} = 16{,}800$).[4] There is therefore greater conjugation between the phenyl rings in biphenylene than in biphenyl as might be expected. There must also be greater conjugation between the phenyl rings in biphenylene than in fluorene, because the 2-position of fluorene is *meta* to a methylene group which in detritiation will *increase* its reactivity by a factor [5] of *ca.* 4, whereas the 2-position of biphenylene is effectively *meta* to a phenyl group which will *decrease* its reactivity by a factor [6] of *ca.* 0·7. If allowance is made for these factors, conjugation between the aryl rings is clearly the greater for biphenylene and cannot be affected to any great extent by steric strain which exists in the molecule.*

The 1-position of biphenylene has almost the same reactivity as the corresponding 2-position in biphenyl ($f^{2\text{-Ph}} = 98$).[3] It is therefore noteworthy that localisation energies predict that the 1-position of biphenylene should have a very similar reactivity to a

* The factors used apply in a trifluoroacetic acid–aqueous perchloric acid medium at 25°. However, the spread of rates under these and the present conditions are very similar, especially for substituents which have a low demand for polarisability effects (cf. ref. 2). Even if each factor were in error by as much as 100%, the conclusions drawn would be unchanged.

[1] Streitweiser and Schwager, *J. Amer. Chem. Soc.*, 1963, **85**, 2855.
[2] See Baker, Bott, Eaborn, and Greasley, *J.*, 1964, 627, and earlier Papers in this series.
[3] Baker, Bott, and Eaborn, *J.*, 1963, 2136.
[4] Baker, Eaborn, and Sperry, *J.*, 1962, 2382.
[5] Eaborn and Taylor, *J.*, 1960, 3301.
[6] Eaborn and Taylor, *J.*, 1961, 1012.

2-position in biphenyl.[7] However, on the basis of localisation energies, the 2-position of biphenylene is then about twenty times more reactive than expected. Dewar values on the other hand, predict a relative reactivity for the 1- and 2-positions of biphenylene very close to that observed, but do not predict such a similar reactivity for the 2-position of biphenyl and the 1-position of biphenylene.[8]

The relative reactivities of the two positions of biphenylene in detritiation in anhydrous trifluoroacetic acid at 70° is 135. This contrasts with the value of 64 obtained by Streitweiser and Schwager who used a medium and temperature similar to that used in our earlier detritiation studies [6] and which gives a smaller spread of rates. The difference in the relative reactivities of the two positions is thus qualitatively in agreement with the variation in rate spread in the two media.

The attempted preparation of 2-tritiobiphenylene by cross-metallation of 2-bromobiphenylene with n-butyl-lithium followed by hydrolysis with tritiated water gave a product which contained *ca.* 10% of tritium in the 1-position. Some metallation therefore readily occurs in the 1-position, a fact which appears to be previously unrecorded.

Experimental.—Anhydrous trifluoroacetic acid was prepared as described previously [9] and was stored under nitrogen after degassing. A solution of once-distilled 2-bromobiphenylene [10] (2·3 g., 0·011 mole) in dry ether (15 ml.) was added to a solution of n-butyl-lithium prepared from n-butyl bromide (1·7 g., 0·012 mole) and lithium (0·18 g., 0·039 g.-atom) in ether (50 ml.). The resulting aryl-lithium was filtered from excess of lithium and hydrolysed with tritiated water (0·2 ml., 60 mc./g. activity). During the usual working-up procedure, inactive biphenylene (0·5 g.) was added to facilitate handling, and the product was steam-distilled to give tritiated biphenylene, m. p. 111—112°.

Kinetic studies were carried out as previously described,[5] with the following modifications: (i) Tritium contents were measured on an I.D.L. scintillation counter, Type 6012. The greater sensitivity of this instrument than that previously used permitted the use of smaller quantities of aromatic compound relative to acid, so that corrections for back reaction were unnecessary. (ii) The reaction tubes were sealed under nitrogen to eliminate oxidative side reactions which occurred in the presence of oxygen and which were apparent from the darkening of the reaction solutions with time. (iii) Tritiated biphenylene prepared as above was found to contain *ca.* 10% of tritium in the 1-position. This was apparent from kinetic studies in which two first-order reactions were clearly distinguishable with half-lives of *ca.* 1·5 and 200 hr. The slow reaction gave good first-order kinetics, the rate of which when calculated permitted a correction to be applied to the fast reaction which then also gave good first-order kinetics. Biphenylene with tritium in both positions was also prepared by refluxing biphenylene with trifluoroacetic acid containing hydrochloric acid and tritiated water. This compound gave kinetics identical, within experimental error, to those obtained with the tritiated biphenylene prepared by cross-metallation. Kinetic runs were triplicated and the average rate constants of $k_1 = 9{\cdot}8 \times 10^{-7}$ sec.$^{-1}$ and $k_2 = 1327 \times 10^{-7}$ sec.$^{-1}$ were reproducible to better than $\pm 5\%$.

We thank the Royal Society for the loan of apparatus from the Government Grant-in-Aid, and for a grant for Scientific Research in Schools to one of us (J. M. B.). We thank also Professor C. Eaborn for helpful advice.

CHEMICAL LABORATORY,
UNIVERSITY OF SUSSEX, BRIGHTON, SUSSEX.
THE COLLEGE, EASTBOURNE, SUSSEX.

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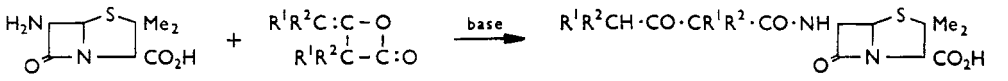
[7] Brown, *Trans. Faraday Soc.*, 1950, **46**, 146; Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553.
[8] Streitweiser, "Moleeular Orbital Theory," Wiley and Sons, Inc., New York, 1961, p. 345.
[9] Baker, Eaborn, and Taylor, *J.*, 1961, 4927.
[10] Baker, Barton, and McOmie, *J.*, 1958, 2672.

889. *The Reaction of Keten Dimers with 6-Aminopenicillanic Acid.*

By A. B. A. Jansen and P. J. Stokes.

6-Aminopenicillanic acid (I) has been acylated to penicillins by use of acid chlorides,[1] alkyl carbonic anhydrides,[1a,2] and dicyclohexylcarbodi-imide.[3] These methods were inapplicable, however, to formation of 6-dioxoalkylaminopenicillanic acids (*e.g.*, III), of interest because the electron-attracting carbonyl group might confer stability on the molecule in acid media,[4] and α-substituents, particularly if bulky, could afford some protection against staphylococcal penicillinase.[1b,5] We therefore examined the reaction of keten dimers (II) with 6-aminopenicillanic acid and found that this provided a convenient route to the desired penicillins (Table 1). In Table 2 comparison is made of their activity with that of potassium benzylpenicillin against resistant strains of *Staphylococcus aureus*.



(I) (II) (III)

The monoalkylketen dimers (I; R^1 = Alk, R^2 = H) were prepared by treatment of the appropriate acid chlorides with triethylamine.[6] It was not possible to prepare keten dimers, substituted by groups other than alkyl, by this route. Dimethylketen dimer

Table 1.

No.	R^1	R^2	Solvent	Yield (%)	$[\alpha]_D^{23.5}$	(*c* in H_2O)	Formula	Analysis [a] Found (%) C	H	N	Required (%) C	H	N
1	H	H	aq. C_4H_8O or H_2O	27—59	+271	0·8	$C_{12}H_{15}KN_2O_5S$	42·9	4·2	8·1	42·6	4·5	8·3
2	Me	H	aq. C_4H_8O	32—42	+290	1·1	$C_{14}H_{19}KN_2O_5S,H_2O$	43·9	5·9	7·4	43·7	5·5	7·3
3	Et	H	aq. C_4H_8O	42	+292	1·2	$C_{16}H_{23}KN_2O_5S,\frac{1}{2}H_2O$	47·3	6·4	6·3	47·6	6·6	6·9
4	Pr^n	H	CH_2Cl_2	13—18	+257	0·9	$C_{18}H_{27}KN_2O_5S,\frac{1}{2}H_2O$	50·5	7·1	6·6	50·1	6·5	6·5
5	Pr^i	H	CH_2Cl_2	34—37	+235	0·4	$C_{18}H_{27}KN_2O_5S$	50·8	6·7	6·3	51·2	6·4	6·6
6	Bu^n	H	CH_2Cl_2	30	+204	1·9	$C_{20}H_{31}KN_2O_5S,H_2O$	51·5	7·0	5·8	51·3	7·1	6·0
7	Ph	H	aq. C_4H_8O	44	+160	0·9	$C_{24}H_{23}KN_2O_5S,2\frac{1}{2}H_2O$	53·6	5·0	5·8	53·8	5·3	5·2
8	Me	Me	aq. C_4H_8O	18—25	+263	0·7	$C_{16}H_{23}KN_2O_5S$	48·5	6·1	7·0	48·7	5·9	7·1

[a] All samples were dried at room temperature under high vacuum before analysis. Their infrared spectra showed a band near 5·6 μ characteristic of the β-lactam structure.

(I; $R^1 = R^2$ = Me) was formed by isomerisation of the less reactive 2,2,4,4-tetramethylcyclobutane-1,3-dione with aluminium chloride,[7] and phenylketen dimer by the action of zinc on phenylchloroacetyl chloride.[8]

[1] (*a*) Perron, Minor, Holdrege, Gottstein, Godfrey, Crast, Babel, and Cheney, *J. Amer. Chem. Soc.*, 1960, **82**, 3934; (*b*) Brain, Doyle, Hardy, Long, Mehta, Miller, Nayler, Soulal, Stove, and Thomas, *J.*, 1962, 1445; Doyle, Hardy, Nayler, Soulal, Stove, and Waddington, *ibid.*, p. 1453.
[2] Doyle, Fosker, Nayler, and Smith, *J.*, 1962, 1440.
[3] Hobbs and English, *J. Medicin. Pharmaceut. Chem.*, 1961, **4**, 207.
[4] Doyle, Nayler, Smith, and Stove, *Nature*, 1961, **191**, 1091.
[5] Doyle, Long, Nayler, and Stove, *Nature*, 1961, **192**, 1183.
[6] Sauer, *J. Amer. Chem. Soc.*, 1947, **69**, 2444; Hanford and Sauer, *Org. Reactions*, 1946, **3**, 108.
[7] Hasek, Clark, Elam, and Martin, *J. Org. Chem.*, 1962, **27**, 60.
[8] Baldwin and Roberts, *J. Amer. Chem. Soc.*, 1963, **85**, 2444.

The reactions with 6-aminopenicillanic acid were carried out in water, aqueous tetrahydrofuran, or methylene chloride, with triethylamine as base. The products were isolated as their (usually deliquescent) potassium salts, by precipitation from ether with butanolic potassium 2-ethylhexanoate. n-Propyl-, isopropyl-, and dimethyl-keten dimers afforded

TABLE 2.

Antibacterial activity against resistant strains of *Staphylococcus aureus*. Minimal inhibitory concentration (μg./ml.).

Strain No.	Potassium Benzylpenicillin	Compound No. 1	2	3	4	5	6	7	8
84	12·5	7·8	0·92	0·92	1·95	0·46	0·92	3·9	1·95
96	50	3·9	1·95	1·95	3·9	3·9		3·9	3·9
98	12·5	1·95	0·92	0·92	1·95	1·95		1·95	1·95

penicillin potassium salts, the infrared spectra of which contained spurious bands near 3·15 and 6·4 μ. These bands were also present in the spectrum of the product obtained from n-butylketen dimer when aqueous tetrahydrofuran was used as solvent. The impurity was not identified but could be removed by regeneration of the free acid, extraction into a limited volume of ether, and reprecipitation of the potassium salt.

Experimental.—Typically, a solution of the keten dimer (0·01 mole) in tetrahydrofuran (6 ml.) was added gradually with stirring to an ice-cooled solution of 6-aminopenicillanic acid (2·16 g., 0·01 mole) in a mixture of water (5 ml.) and tetrahydrofuran (10 ml.) containing triethylamine (1·5 ml., 0·01 mole). Stirring was continued for a further hour, then water (15 ml.) was added, and the mixture was extracted with ether (3 × 10 ml.). The aqueous layer was acidified and the liberated acid was collected in ether (2 × 10 ml.). The addition of 2N-butanolic potassium 2-ethylhexanoate (5 ml., 0·01 equiv.) to the dried solution afforded the *potassium salt* as a gum which was obtained as a solid by solution in acetone (3 ml.), followed by reprecipitation with dry ether, and trituration with fresh dry ether. The product was separated by centrifugation.

The obvious modifications were made when water alone was the solvent.

In those reactions in which methylene chloride was used as solvent, two equivalents of triethylamine were used, the solution being prepared in the manner described by Perron and his co-workers.[9] In this case the solvent was removed under reduced pressure at room temperature before the mixture was worked up as described above.

Analytical data and physical constants for the penicillin potassium salts are collected in Table 1.

We thank Mr. J. R. Cousin for interpretations of the infrared spectra, Mr. A. W. Rule for the bioassays, and Miss M. E. Medd for experimental assistance.

RESEARCH LABORATORIES, JOHN WYETH AND BROTHER LTD.,
NEW LANE, HAVANT, HANTS.

[*Received, March 9th*, 1964.]

[9] Perron, Minor, Crast, and Cheney, *J. Org. Chem.*, 1961, **26**, 3365.

890. 2-*Acetylbenzimidazole.*

By G. W. H. Cheeseman.

Quinoxalines are commonly prepared from the condensation of *o*-phenylenediamines and αβ-dicarbonyl compounds, but during routine preparations of 2-methylquinoxaline [1] from *o*-phenylenediamine and pyruvaldehyde, a high-melting by-product was also obtained. This has now been shown to be 2-acetylbenzimidazole; it has the expected amphoteric properties, readily gives a positive iodoform reaction, and shows NH absorption at 3300 cm.$^{-1}$ and carbonyl absorption at 1670 cm.$^{-1}$. 2-Acetylbenzimidazole was characterised by the preparation of its 1-methyl derivative and independently synthesised by chromium trioxide oxidation of (±)-2-1′-hydroxyethylbenzimidazole.

It appears most probable that 2-acetylbenzimidazole is formed by preferential condensation of the aldehyde group of pyruvaldehyde with *o*-phenylenediamine followed by oxidation of the resulting dihydrobenzimidazole. Both pyruvic and lactic acids are possible impurities in the pyruvaldehyde which was used as a 30% aqueous solution. Pyruvic acid condenses with *o*-phenylenediamine to give 2-hydroxy-3-methylquinoxaline in excellent yield; [2] lactic acid condensation furnishes (±)-2-1′-hydroxyethylbenzimidazole.[3] It is possible that the latter might be oxidised to 2-acetylbenzimidazole under the conditions of the reaction.

Both 2-acetyl- and 2-benzoyl-benzimidazole show ultraviolet absorption maxima closely similar to those of their respective 1-methyl derivatives. The n.m.r. spectrum of 2-acetyl-1-methylbenzimidazole shows unsplit O–CH_3 and N–CH_3 absorptions at τ 7·25 and 5·88. The N–CH_3 absorption of 2-benzoyl-1-methylbenzimidazole is at τ 5·97, both spectra show additional complex aromatic proton absorption.

Experimental.—Infrared spectra were measured for Nujol mulls on a Perkin-Elmer model 137 instrument. Ultraviolet spectra were measured for 96% ethanol solutions in a Perkin-Elmer model 137 UV instrument.

Reaction of o-Phenylenediamine and Pyruvaldehyde. *o*-Phenylenediamine (135 g., 1·25 mole), 30% pyruvaldeyde (310 g., 1·29 mole), and sodium metasulphite (245 g., 1·29 mole) were caused to react as described by Jones and McLaughlin.[1] The product was isolated in ether and the extract dried (Na_2SO_4) and evaporated. Distillation at 0·7 mm. gave 2-methylquinoxaline (153 g., 85%), b. p. (mainly) 82—83°. The distillate crystallised on cooling but discoloured on storage. Trituration of the residue from the distillation with benzene gave *2-acetylbenzimidazole* (6·1 g., 3%), m. p. (mainly) 187—189 raised to 189—190° by crystallisation from benzene (Found: C, 67·6, 67·7; H, 4·9, 5·1; N, 17·35, 17·45. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%); $\lambda_{max.}$ 237, 241 (inflexion), and 304 mμ; ν 3300 (NH) and 1670 cm.$^{-1}$ (C=O).

2-Acetylbenzimidazole. A solution of chromium trioxide (1·5 g., 0·015 mole) in water (5 ml.) was added dropwise to a solution of (±)-2-1′-hydroxyethylbenzimidazole [3] (3·24 g., 0·02 mole) in glacial acetic acid (15 ml.) at 90°. The reaction mixture was heated at 100° for a further 5 min. and then poured into water (*ca.* 200 ml.). A flocculent precipitate was discarded. The filtrate was extracted with chloroform, and the combined extracts dried (Na_2SO_4) and evaporated. Crystallisation of the residue from benzene (60 ml.), gave 2-acetylbenzimidazole (2·0 g., 63%), m. p. (mainly) 188—189° not depressed on admixture with a sample obtained as described above.

2-Acetyl-1-methylbenzimidazole. Methyl sulphate (1·26 ml., 0·013 mole) was added to a solution of 2-acetylbenzimidazole (1·6 g., 0·01 mole) in 2N-sodium hydroxide (15 ml.). A precipitate formed rapidly and after cooling to 0°, *2-acetyl-1-methylbenzimidazole* (0·90 g., 52%), m. p. 74—75°, was filtered off. The m. p. was unchanged by crystallisation from aqueous methanol (Found: C, 68·8; H, 5·8. $C_{10}H_{10}N_2O$ requires C, 68·9; H, 5·8%); $\lambda_{max.}$ 237, 241 (inflexion), and 304 mμ; ν 1680 cm.$^{-1}$ (C=O). The *oxime*, prepared in acetate buffer, and

[1] Jones and McLaughlin, *Org. Synth.*, 1950, **30**, 88.
[2] Hinsberg, *Annalen*, 1896, **292**, 245.
[3] Phillips, *J.*, 1928, 2393.

crystallised first from a little methanol and then from benzene had m. p. 218—219° (Found: C, 63·7; H, 6·2. $C_{10}H_{11}N_{30}$ requires C, 63·5; H, 6·9%).

2-*Benzoylbenzimidazole*. A sample prepared by Bistrycki and Przeworski's method [4] had m. p. 215—216° (recorded 209—210°); $\lambda_{max.}$ 267 and 322 mμ.

2-*Benzoyl*-1-*methylbenzimidazole*. This was prepared similarly, in 72% yield. Crystallisation from aqueous ethanol gave needles, m. p. 70—71° (Found: C, 76·2; H, 5·45. Calc. for $C_{15}H_{12}N_2O$: C, 76·3; H, 5·1%); $\lambda_{max.}$ 267 and 318 mμ; ν 1660 cm.$^{-1}$ (C=O). Agarwal and Seshadri [5] give m. p. 70—71°; $\lambda_{max.}$ 265 and 306 mμ (in methanol); ν 1661 cm.$^{-1}$ (C=O).

We thank Professor H. Burton for his encouragement and the University of London for a grant from the Central Research Fund. N.m.r. spectra were measured at Queen Mary College, London E.1, through the courtesy of Professor B. C. L. Weedon and Dr. M. F. Ansell.

QUEEN ELIZABETH COLLEGE (UNIVERSITY OF LONDON),
LONDON W.8.

[*Received, March 2nd*, 1964.]

[4] Bistrycki and Przeworski, *Ber.*, 1912, **45**, 3492.
[5] Agarwal and Seshadri, *Tetrahedron*, 1964, **20**, 17.

891. *Preparation of* 3-*Aminohydantoins.*

By J. S. DAVIDSON.

THE published synthesis of 3-aminohydantoins [1,2] is somewhat tedious. A simpler preparation is now described. On refluxing hydrazine hydrate with the readily accessible 5,5-disubstituted hydantoins, ammonia was evolved, and 3-aminohydantoins were obtained.

Experimental.—The hydantoin was dissolved in twice its weight of hydrazine hydrate (64% N_2H_4), the mixture refluxed for several hours, cooled, the solid product filtered off, washed with water, and recrystallised from water or ethanol. In this way the following 3-aminohydantoins were obtained: 5,5-Dimethyl- (6 hr.; 6%, but see below), needles (from water), m. p. 177—178° (Found: N, 29·3. Calc. for $C_5H_9N_3O_2$: N, 29·4%), *benzylidene derivative*, m. p. 178° (Found: C, 62·2; H, 5·8. $C_{12}H_{13}N_3O_2$ requires C, 62·3; H, 5·6%), p-*methoxybenzylidene derivative*, m. p. 161° (Found: C, 59·9; H, 6·0; N, 16·0. $C_{13}H_{15}N_3O_3$ requires C, 59·7; H, 5·7; N, 16·1%). 5-Ethyl-5-methyl- (17 hr., 12%) (needles from water), m. p. 152—153° (Found: N, 27·0. Calc. for $C_6H_{11}N_3O_2$: N, 26·8%), *benzylidene derivative*, m. p. 137—138° (Found: C, 64·0; H, 6·4. $C_{13}H_{15}N_3O_2$ requires C, 63·7; H, 6·15%). 5,5-Diethyl- (24 hr., 51%) (needles from water), m. p. 178—179° (Found: N, 24·9. Calc. for $C_7H_{13}N_3O_2$: N, 24·6%). 5-*Methyl*-5-n-*nonyl*- (24 hr., 44%) (plates from ethanol), m. p. 137—138° (Found: N, 16·4. $C_{13}H_{25}N_3O_2$ requires N, 16·5%). 5-Ethyl-5-phenyl- (19 hr., 51%) (bunched needles from ethanol), m. p. 156—157° (Found: N, 19·3. Calc. for $C_{11}H_{13}N_3O_2$: N, 19·15%), *benzylidene derivative*, m. p. 172—173° (Found: C, 70·0; H, 5·8. $C_{18}H_{17}N_3O_2$ requires C, 70·4; H, 5·5%). 5,5-Diphenyl- (6 hr., 38%) (needles from ethanol), m. p. 195—196° (Found: N, 15·7. Calc. for $C_{15}H_{13}N_3O_2$: N, 15·7%).

If the reaction time was unduly prolonged the yield decreased and carbohydrazide was formed. Treatment of the aqueous mother-liquor with benzaldehyde then gave dibenzylidenecarbohydrazide (needles from ethanol), m. p. 201—202°.

Optimum conditions have not been extensively examined, especially as regards isolation of the product. The poor yields of the lower members of the series are undoubtedly due to high water solubility. Thus, in the case of the 5,5-dimethyl compound, the benzylidene derivative could be isolated in 49% yield from the reaction liquors. This afforded the aminohydantoin

[1] Taub B.P. 764,146/1956.
[2] Schlögl, Derkosch, and Wawersich, *Monatsh.*, 1954, **85**, 607, and later Papers.

in 22% overall yield by steam distillation with hydrochloric acid, neutralisation with sodium hydrogen carbonate, evaporation to dryness, and recrystallisation of the product from n-butanol.

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

[*Received, March 2nd,* 1964.]

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892. *Preparation of Standard Chromium*(II) *Solutions from High-purity Metal.*

By J. M. CRABTREE.

CHROMIUM(II) solutions are powerful reducing agents and are frequently used in volumetric analysis,[1] in the determination of organic substances,[2] in kinetic studies of electron-transfer reactions,[3] in studies of chromium(II) complexes,[4] and in the preparation of chromium(III) compounds.[5]

Usual methods for preparation of chromous solutions are (i) reduction of acid chromium(III) solutions with amalgamated zinc in a Jones reductor,[1] often followed by precipitation of chromous acetate as a first stage in preparing other chromium(II) salts; (ii) electrolytic reduction of chromic chloride or perchlorate; [6] (iii) dissolution of chromium metal in hot oxygen-free hydrochloric acid.[7]

These methods have drawbacks in that they may take many hours for completion, foreign ions such as zinc or acetate may contaminate the chromous solutions, or the solutions may be non-standard with respect to chromium(II) or acid.

A simple method for the preparation of highly pure standard chromium(II) solutions involving only the pure metal and cold dilute acid is described here. When spectrographically pure chromium flake is placed in 0·3N-hydrochloric acid (deoxygenated) no reaction occurs during 24 hours or even on boiling the solution. However, if a metal flake is broken with a glass rod under the solution, reaction begins after a short induction period of a few minutes and rapidly goes to completion at room temperature. Other, unbroken, metal flakes in the solution also start reacting with the acid on coming into contact with metal already dissolving.

It seems that an oxide film prevents dissolution, for if a flake is broken in air and immediately placed in the acid solution no reaction occurs even on heating.

These facts are consistent with a mechanism requiring a chromium metal–chromic oxide couple for initiation of the reaction. When one flake is broken the pieces move rapidly through the solution due to hydrogen evolution; they come into contact with unbroken flakes and form a metal–metal oxide couple so that the unbroken flakes begin to dissolve. Complete dissolution therefore occurs if the flakes have free movement through the solution. The initiation of a reaction by destruction of a protective oxide film is well known in corrosion chemistry.[8]

Experiments with other acids showed that 0·3N-perchloric acid and 0·3N-sulphuric acid do not attack pure chromium flakes until a flake is broken under the solution, whereupon reaction goes to completion in the cold. 0·5N-Nitric acid does not react at all, which is not

[1] Vogel, "Quantitative Inorganic Analysis," 3rd edn., Longmans, London, 1961, p. 340.
[2] Bottei, *Analyt. Chim. Acta*, 1964, **30**, 6.
[3] Taube, *Canad. J. Chem.*, 1959, **37**, 129.
[4] Pecsok, Shields, and Schaeffer, *Inorg. Chem.*, 1964, **3**, 114.
[5] Dwyer, "Advances in the Chemistry of the Coordination Compounds," Macmillan, New York, 1961, p. 21.
[6] Pecsok and Schaeffer, *J. Amer. Chem. Soc.*, 1961, **83**, 62.
[7] Pecsok and Bjerrum, *Acta Chem. Scand.*, 1957, **11**, 1419.
[8] Chilton, "Principles of Metallic Corrosion," Royal Institute of Chemistry Monographs for Teachers," No. 4, 1961.

surprising considering the passive nature of other metals such as iron in nitric acid solutions. The chromic oxide film is penetrated when more concentrated acid (~2N) is used and 1N-hydrochloric acid reacts on heating.

Chromium(II) solutions are on the edge of thermodynamic instability towards oxidation by hydrogen ion; the oxidation-reduction potential at 25° of Cr^{2+}/Cr^{3+} is −0·41 v and that of the hydrogen couple in water at pH 7 is −0·414 v. However the solutions are kinetically stable in the absence of more concentrated acid, noble-metal catalysts, or impurities. Thus solutions prepared as outlined here and stored under nitrogen may be kept for at least several months without appreciable oxidation and do not deteriorate as do chromous solutions prepared using zinc amalgam.

Experimental.—A known weight of high-purity chromium flake (Johnson, Matthey and Co. spectrographically standardised flake is excellent but unfortunately is no longer available; electrolytically-pure metal from Union Carbide Ltd. is satisfactory if very thin flakes, *i.e.*, ~$\frac{1}{32}$ inch thick, are selected) is placed in a sieved glass container at the bottom of a three-necked flask. This sieved container is fitted with a glass plunger through a neck of the flask and serves as a convenient "flake-breaker."

A known volume of 0·3N-acid (AnalaR HCl, $HClO_4$, or H_2SO_4) is pipetted into the flask. Purified nitrogen is passed through the solution for several hours to remove traces of oxygen and then the reaction may be initiated by breaking some of the metal flakes with the glass plunger. Using 0·5201 g. of Matthey flake and 100 ml. of 0·3N-hydrochloric acid, dissolution is complete in about 2½ hr. yielding a clear sky-blue solution of 0·1M-$CrCl_2$ + 0·1N-HCl. Excess of acid is necessary to ensure complete dissolution and to prevent hydrolysis of the aquochromium(II) ion. This stock solution may be readily diluted with deoxygenated water and transferred to a storage burette by nitrogen pressure.

Chromium(II) concentrations were checked by titration with potassium iodate.[9] No chromium(III) was detected spectrophotometrically or by difference between total chromium and chromium(II) content.

Gifts of chromium metal from Johnson, Matthey & Co., and Union Carbide, Ltd., are gratefully acknowledged.

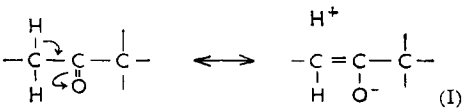
CHEMISTRY DEPARTMENT,
WELSH COLLEGE OF ADVANCED TECHNOLOGY, CARDIFF. [*Received, March 2nd,* 1964.]

[9] Stone, *Analyt. Chem.*, 1948, **20**, 747.

893. *Long-range Coupling in Ketones and their Complexes.*

By P. N. GATES and E. F. MOONEY.

LONG-RANGE proton–proton coupling is normally, although not necessarily, associated with conjugated or pseudo-conjugated systems.[1] The presence of long-range coupling in dialkyl ketones has been reported,[2] and this coupling is attributed to the electromeric effect of the



(I)

electronegative carbonyl group, which causes activation of the α-C–H bonds, *i.e.*, contribution from (I).

[1] Snyder and Roberts, *J. Amer. Chem. Soc.*, 1962, **84**, 1582.
[2] (*a*) van Meurs, *Spectrochim. Acta*, 1963, **19**, 1695; (*b*) Gerrard and Mooney, Paper B1/9, XIXth I.U.P.A.C. Meeting, London, July 1963.

On complex-formation between benzyl methyl ketone and boron trifluoride it was reported [2b] that the long-range coupling, between the α-CH_3 and α′-CH_2 groups, increased from 0·5 to 0·95 c./sec. To investigate the variation of the coupling constant with acceptor molecules of increasing Lewis-acid strength, the complexes of ethyl methyl ketone with $TiCl_4$, BF_3, and $SbCl_5$ have been investigated. These three metal halides were chosen since previous infrared studies [3] of their complexes with xanthone had, from consideration of the carbonyl shift, not only placed the order of acceptor strength but shown that the acceptor strengths varied considerably. Table 1 indicates that the long-range coupling constants,

TABLE 1.

Chemical shifts, long-range coupling constants, and carbonyl shifts for $MeCO{\cdot}Et,MX_n$ complexes.

	Ketone	$TiCl_4$		BF_3		$SbCl_5$	
	δ *	δ *	Δδ	δ *	Δδ	δ *	Δδ
α′-CH_3	3·27	2·62	−0·65	2·64	−0·63	2·34	−0·93
α-CH_2	2·92	2·41	−0·51	2·34	−0·58	2·17	−0·75
β-CH_3	4·36	4·12	−0·24	4·12	−0·24	4·05	−0·31
$J_{H\alpha H\alpha'}$ (c./sec.)	0·4	1·0		1·2		1·3	
$\Delta\nu_{C=O}$ (cm.$^{-1}$) †	—	50		65		91	

* Chemical shifts in p.p.m. to high field of CH_2Cl_2. † Measured in CH_2Cl_2 solution.

$J_{H\alpha H\alpha'}$, increase slightly with increasing acceptor strength of the metal halide. However, the differences in $J_{H\alpha H\alpha'}$ are not sufficient to give a reliable order of acceptor strengths, compared to the more definite order obtained by consideration of the carbonyl shifts, and the shifts of the α-CH_2 group to low field on complex-formation. Furthermore, the values of $J_{H\alpha H\alpha'}$ were measured directly from first-order splittings, and owing to the similarity of the chemical shifts of the α′-CH_3 and α-CH_2 groups (Table 1) theoretical treatment (of the eight-spin system) may show that the values of $J_{H\alpha H\alpha'}$ need to be modified; thus, the order may be fortuitous. However, Table 1 clearly indicates that, on complex-formation, there is an increase in the long-range coupling constant, and this certainly supports the hypothesis of the increasing delocalisation of the σ-electrons, in the α-C–H bonds, when the polarisation of the carbonyl group is increased.

Experimental.—Preparation of complexes. The *complexes* of $TiCl_4$ and $SbCl_5$ were prepared by the addition of the metal halide to the ketone in methylene dichloride at −80°. The insoluble complex was filtered off and dried (10 mm.). The BF_3 complex was prepared by saturating a solution of the ketone in light petroleum (b. p. 40—60°) with boron trifluoride gas; the complex was purified by distillation.

TABLE 2.

Preparation of complexes, $MeCO{\cdot}Et,MX_n$.

	Yield	Found (%)			Reqd. (%)		
MX_n	(%)	C	H	X	C	H	X
$TiCl_4$	94	—	—	53·5	—	—	54·2
$SbCl_5$	98	—	—	47·5	—	—	47·8
BF_3 (b. p. 55°/13 mm.)	87	34·2	5·7	40·4	34·3	5·7	40·8

The ^1H resonance spectra were recorded on a Perkin-Elmer n.m.r. spectrometer operating at 40 Mc./sec., using solutions of the ketone and complexes in methylene dichloride. The

[3] Cook, *Canad. J. Chem.*, 1963, **41**, 522.

chemical shifts, in p.p.m. from methylene dichloride, were measured using side-band modulation of the solvent.

The infrared spectra were also recorded in compensated methylene dichloride solutions, using a Grubb–Parsons Spectromaster instrument.

We thank Dr. W. Gerrard for his continued encouragement, and the D.S.I.R. for a grant to purchase the n.m.r. spectrometer.

NORTHERN POLYTECHNIC, HOLLOWAY ROAD, LONDON N.7. [*Received, March 2nd*, 1964.]

894. *The Use of 2-Iodo-1-methylpyridinium Iodide in Amide Synthesis.*

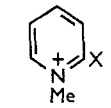
By J. K. SUTHERLAND and D. A. WIDDOWSON.

IN the search for reagents useful in peptide bond formation we have investigated the reaction of 2-iodo-1-methylpyridinium iodide [1] (I) with carboxylate ions in the hope that the intermediate (II) would be formed and would further react with amines forming amides. As shown in the Table equimolar proportions of the salt (I) and carboxylate salts react at

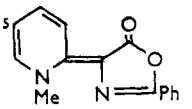
The synthesis of cyclohexylamides from 2-iodo-1-methylpyridinium iodide.

Acid	Base	Solvent	Yield (%)
$PhCO_2H$	Et_3N	Me_2NCHO	53
,,	,,	$MeNO_2$	43
,,	,,	MeCN	70
$Me{\cdot}CO_2H$	NaOH	65% $CH_3{\cdot}CN{-}H_2O$	25

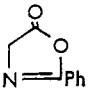
room temperature in a variety of solvents and, after addition of cyclohexylamine, good yields of amides can be isolated. However, when hippuric acid was used in the condensation a red crystalline solid, $C_{15}H_{12}N_2O_2$, was isolated. The compound could be recrystallised to give a yellow form by rapid cooling of an acetonitrile solution whereas slow cooling gave a deep red substance. The two forms have identical m. p.s and i.r. and u.v. spectra in



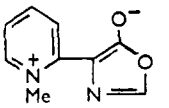
(I : X = I)
(II : X = O·CO·R)
(III : X = O·CO·CH_2·NH·COPh)



(IV)



(V)



(VI)

solution but differed slightly in the i.r. spectra of mulls. From the analytical figures the compound must be derived by a 1 : 1 combination of the reagents. The i.r. spectrum shows no N–H absorption but has peaks at 1680, 1635, 1605, and 1595 $cm.^{-1}$. In the n.m.r. spectrum in dimethyl sulphoxide there are present one *N*-methyl group at τ 5·65 and nine aromatic protons only one of which is completely resolved and appears as a triplet at τ 3·22 (J = 7 c./sec.), each peak being further split into a doublet (J = 1·5 c./sec.). This position and coupling is consistent with it being at C-5 in (IV).[2] On the basis of the above information, (IV) seems the most likely structure for the compound which could be formed

[1] Bradlow and Vanderwerf, *J. Org. Chem.*, 1951, **16**, 1143.
[2] Personal communication from Dr. J. A. Elvidge.

by the collapse of (III) to form the oxazolone (V), the reactive methylene of which would then condense with a further molecule of the salt (I) to give (IV). Degradative experiments were largely unsuccessful but benzamide could be isolated from permanganate oxidation of (IV) [3] indicating that the nitrogen atom of the benzamide group must be attached to an unsaturated carbon atom. However, we were able to prepare the compound by reaction of the oxazolone [4] (V) with the salt (I) under the experimental conditions of the original preparation. The low position of i.r. carbonyl absorption of (IV), its colour, and unreactivity to nucleophiles (no reaction with cyclohexylamine in refluxing acetonitrile) all suggest a considerable contribution of the dipolar resonance hybrid (VI) to the structure of (IV).

Experimental.—Preparation of N-cyclohexylamides. The pyridinium salt (I) (347 mg.), benzoic acid (122 mg.), and triethylamine (0·15 ml.) were stirred in acetonitrile (10 ml.) for 15 min. Cyclohexylamine (0·12 ml.) was added and there was an immediate precipitation. After a further 15 min. the solvent was removed *in vacuo* and the residue triturated with water. The precipitated *N*-cyclohexylbenzamide (140 mg.), m. p. 148—151°, was recrystallised from ethyl acetate.

The reaction of hippuric acid with the pyridinium salt (I). (*a*) To a mixture of the pyridinium salt (I) (694 mg.) and hippuric acid (177 mg.) in dimethylformamide (10 ml.), triethylamine (0·28 ml.) was added. After 1 hr. the mixture was poured into water. The red precipitate (87 mg.) was filtered off and recrystallised from acetonitrile to give the *oxazolone* (IV), m. p. 227—229° $\lambda_{max.}$ (in MeOH) 350 mμ (ε 1670) and 427 mμ (ε 2010) (Found: C, 71·7; H, 5·0; N, 11·2. $C_{15}H_{12}N_2O_2$ requires C, 71·4; H, 4·8; N, 11·1%).

(*b*) The pyridinium salt (II) (224 mg.) and the oxazolone (V) (103 mg.) were dissolved in dimethylformamide (5 ml.), and triethylamine (0·15 ml.) added. The oxazolone (IV) (88 mg.) was obtained and shown to be identical to that above by m. p., mixed m. p., and comparison of i.r. spectra.

Permanganate oxidation of the oxazolone (IV). A 3% aqueous solution of potassium permanganate was added dropwise to (IV) (102 mg.) in 2N-sulphuric acid (20 ml.) at 90°. When the permanganate colour became permanent the solution was basified, cooled, and extracted with ether. Concentration of the extract gave benzamide.

We thank the D.S.I.R. (D. A. W.) and the Chemical Society for financial support.

IMPERIAL COLLEGE, LONDON S.W.7. [*Received, January 22nd*, 1964.]

[3] We thank Mr. J. A. Burgess for these experiments.
[4] Cornforth, " The Chemistry of Penicillin, Princeton University Press, 1949, p. 778.

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895. *The Reaction of α-Chlorobenzaldoxime with Carboxylate Ions.*

By J. K. SUTHERLAND and D. A. WIDDOWSON.

IN the search for active esters useful in peptide syntheses acyl derivatives of *N*-hydroxyphthalimide have proved to be reactive acylating agents.[1] More recently the esters of *N*-hydroxysuccinimide have been found to have similar properties.[2] However, these acyl derivatives are rather tedious to prepare, requiring condensing agents which themselves can be used for peptide bond formation. *O*-Acylhydroxamic acids should have similar properties and a simple preparation of *ON*-dibenzoylhydroxylamine (III) from α-chlorobenzaldoxime (I) and silver benzoate has been described.[3] In repeating this work we

[1] Nefkens and Tesser, *J. Amer. Chem. Soc.*, 1961, **83**, 1263.
[2] Anderson, Zimmerman, and Callahan, *J. Amer. Chem. Soc.*, 1963, **85**, 3039.
[3] Werner and Skiba, *Ber.*, 1899, **32**, 1654.

have confirmed the formation of (III) but have found no evidence for the formation of (II) as an isolable intermediate, in contrast to the original work.

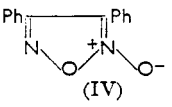
$$\underset{\text{(I)}}{PhCCl{=}N{\cdot}OH} \longrightarrow \underset{\text{(II)}}{PhC(O{\cdot}COPh){=}N{\cdot}OH} \longrightarrow \underset{\text{(III)}}{PhCO{\cdot}NH{\cdot}O{\cdot}COPh}$$

We have also examined this condensation reaction with sodium, triethylammonium, and tetraethylammonium salts in a variety of anhydrous solvents and aqueous mixtures. The yields of the acylhydroxamates are shown in the Table. In cases where triethylamine

Reaction of carboxylate ions with α-chlorobenzaldoxime at room temperature.

Acid	Base	Solvent	Yield (%)
$PhCO_2H$	Et_4NOH	MeCN	60
,,	,,	Me_2NCHO	43
,,	,,	Dioxan	43
,,	,,	t-BuOH	58
,,	,,	PhH	66
$PhCO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$	NaOH	33% MeCN–H_2O	34
,,	,,	20% ,,	43
$MeCO_2H$	Et_3N	$MeNO_2$	10
$PhCO_2H$	,,	MeCN	48

was used as the base in anhydrous solvents and sodium hydroxide in mixed aqueous solution the balance of the reagents was isolated as diphenylfuroxan (IV) and unchanged carboxylic acid. In these examples the reaction mixture must have been basic enough to dehydrochlorinate (I) to benzonitrile oxide which then dimerises to (IV).[4] Where the tetraethylammonium salts were used in anhydrous solvents a mixture of benzoic acid and unchanged carboxylic acid was isolated along with the acylhydroxamate. No diphenylfuroxan was formed. In the hope of improving the yields we studied, in some detail, the reaction of tetraethylammonium benzoate with (I) in dimethylformamide. After the initial mixing of reagents a small amount of a gas (not carbon dioxide) was evolved and, on evaporation of the solvent, only the acylhydroxamate, benzoic acid, and tetraethylammonium chloride were found. In particular no benzhydroxamic acid could be detected by the sensitive ferric chloride test. Having previously observed that reaction of *N*-benzoyl-*O*-cyclohexanecarbonylhydroxylamine with nitrosating agents converts it into a mixture of cyclohexanecarboxylic and benzoic acids with the evolution of nitrous oxide [5] we tested the reaction mixture above for nitrosating species with Griess's reagent.[6] The test was positive so it is possible that some acylhydroxamate is destroyed by an unspecified nitrosating intermediate. We have excluded benzonitrile oxide as an intermediate in the formation of either (II) or (III) since it does not react with carboxylic acids under our experimental conditions. Variation of the molar ratios of the reactants has little effect on the yield, calculated from the reactant present in smallest proportion, suggesting that intermediate anhydride formation is of little importance.


(IV)

The acylhydroxamate formed in the condensation can be condensed with an amine *in situ*; thus tetraethylammonium hippurate was treated with α-chlorobenzaldoxime in acetonitrile and, after two hours, cyclohexylamine was added. The *N*-cyclohexylamide of hippuric acid was formed in 26% yield. However *ON*-dibenzoylhydroxylamine reacts only slowly with cyclohexylamine at room temperature in nitromethane. On refluxing the solution, *N*-cyclohexyl-*N'*-phenylurea was formed, obviously from phenyl isocyanate formed by Lossen rearrangement [7] of the diacyl compound. This rearrangement must be

[4] Werner and Buss, *Ber.*, 1894, **27***B*, 2193.
[5] Unpublished observation Qurreshi and Sutherland.
[6] Griess, *Ber.*, 1879, **12**, 427.
[7] Lossen, *Annalen*, 1875, **175**, 320.

base catalysed since the Lossen rearrangement did not occur in the absence of cyclohexylamine.

1-Benzoyloxy-2-pyridone proved to be a reactive acylating agent but attempts to prepare this type of ester by reaction of benzoate ion with 2-chloro-, 2-iodo-, and 2-chloro-4-nitropyridine 1-oxides failed because of the unreactivity of the pyridines.

Experimental

Experimental.—Preparation of salts. Trimethylammonium salts were prepared *in situ* by addition of triethylamine, sodium salts by titration with N-sodium hydroxide, and tetraethylammonium by addition one equivalent of 26·5% w/v tetraethylammonium hydroxide in water followed by evaporation to dryness *in vacuo*.

Typical preparation of diacylhydroxylamine. Hippuric acid (3·6 g.) was neutralised with 1N-sodium hydroxide (20 ml.), and the pH adjusted to 7 with acid. A solution of α-chlorobenzaldoxime (3·11 g.) in acetonitrile (5 ml.) was added dropwise to the aqueous solution with stirring. After 3 hr. the precipitate was filtered off, dried, and crystallised from ethanol to give N-*benzoyl*-O-*hippurylhydroxylamine* (2·56 g.; 43%), m. p. 181—182° (decomp.); $\nu_{max.}$ 3300, 3150, 1805, 1650 cm.$^{-1}$, $\lambda_{max.}$ (in EtOH) (223 mμ (ε 14,400) (Found: C, 64·7; H, 4·9; N, 9·2. $C_{16}H_{14}N_2O_4$ requires C, 64·4; H, 4·7; N, 9·4%).

Preparation of N-*cyclohexylhippuramide.* The tetraethylammonium salt of hippuric acid (1·48 g.) and α-chlorobenzaldoxime (1·27 g.) were dissolved in acetonitrile (10 ml.). After 12 hr. cyclohexylamine (1 ml.) was added with cooling. 1 hr. later most of the solvent was removed, water added, and the mixture extracted with chloroform. Evaporation of the chloroform gave a solid which was crystallised from benzene to give N-*cyclohexylhippuramide* (540 mg.; 26%), m. p. 165°; $\nu_{max.}$ 3300, 1665, 1640 cm.$^{-1}$ (Found: C, 69·4; H, 7·8; N, 10·8. $C_{15}H_{20}N_2O_2$ requires C, 69·25; H, 7·7; N, 10·4%).

Reaction of ON-*dibenzoylhydroxylamine with cyclohexylamine.* The diacyl compound (500 mg.) in nitromethane (10 ml.) containing cyclohexylamine (630 mg.) was refluxed for 2 hr. The mixture was poured into water, extracted with ether, and the ethereal extract concentrated to give a solid which on crystallisation from aqueous ethanol gave *N*-cyclohexyl-*N'*-phenylurea, m. p. 187—189°, identical with an authentic specimen prepared from phenyl isocyanate and cyclohexylamine.

When the reaction was carried out for 20 hr. at room temperature the urea was also obtained. No reaction occurred in the absence of cyclohexylamine.

Preparation of 1-*benzoyloxy*-2-*pyridone.*—1-Hydroxy-2-pyridone [8] (500 mg.) in water was neutralised (phenolphthalein) with 0·1N-potassium hydroxide. The solution was evaporated to dryness and the potassium salt suspended in dioxan (10 ml.) to which benzoyl chloride (1 ml.) in dioxan (5 ml.) was added. After 30 min. the mixture was poured into water and extracted with chloroform. Concentration of the extract and crystallisation of the residue from benzene gave the *benzoate* (770 mg.), m. p. 143—144° (Found: N, 6·6; $C_{12}H_9NO_3$ requires N, 6·5%).

Reaction of the ester with cyclohexylamine in acetonitrile or nitromethane gave *N*-cyclohexylbenzamide in 98% yield.

We thank the D.S.I.R. (D. A. W.) and the Chemical Society for financial support.

Imperial College, London S.W.7. [*Received, January 22nd*, 1964.]

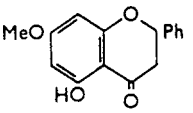
[8] Newbold and Spring, *J.*, 1948, 1864.

896. *Pinostrobin and Alpinetin from* Kaempferria pandurata.

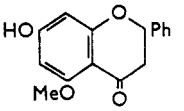
By Stang Mongkolsuk and F. M. Dean.

The plant *Kaempferria pandurata* is a member of the ginger family (Zingiberaceae), and is used in Thailand as a constituent of curries and medicinally as an aphrodisiac and a remedy in cases of abnormal blood pressure. Extraction of the dried rhizome gave (±)-pinostrobin (I) together with smaller quantities of (±)-alpinetin (II). Though these flavanones are isomeric, they have not been found together before. Pinostrobin [1] is common amongst *Pinus* species (Pinaceae) and also occurs in some species of *Prunus* (Rosaceae), but alpinetin [2] is a rare compound previously isolated only from *Alpinia chinensis* which, however, is also a member of the Zingiberaceae.

Flavonoids seldom possess a 5-methoxyl group while there are free hydroxyl groups at other positions.[3] Examples other than alpinetin are provided by azaleatin [4] (*Rhododendron mucronatum*), vogeletin [5] (*Tephrosia vogelii*) and capensinidin [6] (*Plumbago capensis*). Thus, this unusual methylation pattern does not seem to be associated with any particular family of plants, but appears to be associated with the flora of tropical and sub-tropical rather than those of temperate regions.



(I)



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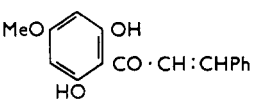

(III)

In the absence of authentic specimens, pinostrobin was identified by its ferric reaction, spectroscopic properties, and proton resonance spectrum as well as by alkaline hydrolysis. This gave first the red salt of chalcone (III) and then, by retro-aldol condensation, benzaldehyde and 2,6-dihydroxy-4-methoxyacetophenone. Alpinetin was identified by its lack of a ferric reaction, its relatively high solubility in dilute alkali, and the identity of its methyl ether with that of pinostrobin.

Experimental.—Dried powdered rhizomes (800 g.) of *Kaempferria pandurata* were continously extracted for 4 days with ether and the extract was concentrated to 600 ml. The yellow solid (2 g.) which slowly separated crystallised from methanol (charcoal) giving alpinetin in needles, m. p. 220° (lit.,[2] 223°), $\lambda_{max.}$ (MeOH) 213 and 283 mμ ($\varepsilon \times 10^{-4}$ 1·8, 1·3); $\nu_{max.}$ (Nujol) 3500 and 3300 (OH, intermolecular bonding) and 1640 cm.$^{-1}$ (conjugated ketone with intermolecular bonding). Methylated by methyl sulphate (2 ml.) and potassium carbonate (10 g.) in boiling acetone (100 ml.) for 5 hr., alpinetin gave the methyl ether as fine needles, m. p. 144° (from methanol), identified with pinostrobin methyl ether by mixed fusion and spectroscopic methods.

After removal of alpinetin, further concentration of the extract furnished pinostrobin, which crystallised from methanol or isopropyl ether in plates (20 g.), m. p. 100° (lit.,[1] 99—100°), $\lambda_{max.}$ (MeOH) 287 mμ ($\varepsilon \times 10^{-4}$ 1·9) with shoulders at 227 and 325 mμ; $\lambda_{max.}$ (MeOH + NaOH) 240, 287, and 335 mμ ($\varepsilon \times 10^{-4}$ 1·6, 1·5, 0·65); $\nu_{max.}$ (Nujol) 1640 cm.$^{-1}$ (chelated ketone), giving an intense red ferric reaction in ethanol [Found: C, 70·8, 70·9, 71·2; H, 5·3, 5·2, 5·3; OMe, 11·0,

[1] Karrer, "Konstitution und Vorkommen der organischen Pflanzenstoffe," Birkhauser Verlag, Basel und Stuttgart, 1958, p. 635.
[2] Kimura, *J. Pharm. Soc. Japan*, 1940, **60**, 151.
[3] Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, Tables 8—12, 14, 15, 17, and 21—26.
[4] Wada, *J. Amer. Chem. Soc.*, 1956, **78**, 4725.
[5] Rangaswami and Rao, *Proc. Indian Acad. Sci.*, 1959, **49**A, 241.
[6] Harborne, *Arch. Biochem. Biophys.*, 1962, **96**, 171.

11·4%; *M* ($CHCl_3$ thermistor), 280. Calc. for $C_{15}H_{11}O_3$·OMe: C, 71·1; H, 5·2; OMe, 11·5%; *M*, 270].

Methylation as for alpinetin gave the methyl ether which separated from methanol in needles, m. p. 144°; $\lambda_{max.}$ (MeOH) 212·5 and 283 mμ ($\varepsilon \times 10^{-4}$ 1·8, 1·3); $\nu_{max.}$ (Nujol) 1670 cm.$^{-1}$ (conjugated ketone) [Found: C, 71·8; H, 5·7; OMe, 21·4, 21·6. Calc. for $C_{15}H_{10}O_2(OMe)_2$: C, 71·8; H, 5·6; OMe, 21·8%].

Pinostrobin (2 g.) was heated under nitrogen with 10% aqueous sodium hydroxide (70 ml.) for 1 hr., and the mixture was then distilled until about 20 ml. had been collected. Treatment of the distillate with 2,4-dinitrophenylhydrazine in hydrochloric acid gave benzaldehyde 2,4-dinitrophenylhydrazone as orange needles, m. p. and mixed m. p. 240° (from ethanol). The residue was acidified with hydrochloric acid and extracted with ether. Phenols were removed

P.m.r. spectrum of pinostrobin.

	Relative intensity	Splitting	Assignments
−2·02	1	Singlet	O*H* O=C
2·59	5	Singlet	Ph protons
3·95	2	Singlet	Ar*H* (positions 6 and 8)
4·62	1	Quadruplet (J = 11·5 cp.s.)	O·C*H*·CH_2Ar
6·23	3	Singlet	ArOCH_3
7·05	1	Doublet (J = 11 c.p.s.)	O·CH·CH_2Ar
7·13	1	Doublet (J = 5 c.p.s.)	O·CH·CH_2Ar

from the ether by means of 2N-aqueous sodium hydroxide and recovered by acidification and ether extraction. They formed a red oil that partly solidified when kept. Vacuum distillation of the oil followed by crystallisation from benzene supplied 2,6-dihydroxy-4-methoxyacetophenone as pale yellow needles, m. p. 136—137° (lit.,[7] 136—137°) having a strong red ferric reaction in ethanol.

We thank Lederle Laboratories Inc. and the Rockefeller Foundation for research grants. We also thank Lederle Laboratories Inc. for the proton resonance spectrum and for much other analytical information.

Faculty of Medical Science, University of Medical Science,
Sri Ayuthya Road, Bangkok. [*Received, January 20th*, 1964.]

[7] Kuhn, Löw, and Trischmann, *Ber.*, 1944, **77**, 202.

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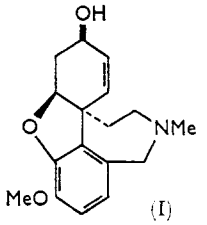
897. *Long-range Proton Coupling in Narwedine and Pummerer's Ketone.*

By G. W. Kirby and H. P. Tiwari.

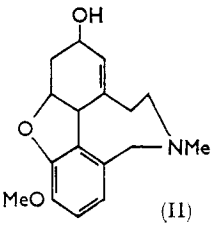
In a recent Paper[1] Bubewa-Iwanowa described the isomerisation of galanthamine (I) by dilute mineral acid to give an alcohol, m. p. 182—184°, assigned the structure (II). We repeated the preparation and obtained an alcohol, m. p. 188—189°, having an infrared spectrum in chloroform identical with that of (±)-epigalanthamine. Oxidation of this substance with manganese dioxide gave (±)-narwedine (III). Dr. Bubewa-Iwanowa kindly compared our specimen with hers and found them identical. She also informed us that, in independent studies, she rejected structure (II) and concluded, in agreement with our results, that the isomerisation product is in fact (−)-epigalanthamine.

[1] Bubewa-Iwanowa, *Chem. Ber.*, 1962, **95**, 1348.

In the course of this work we examined the nuclear magnetic resonance (n.m.r.) spectrum of (±)-narwedine (III). The α-(4·00 τ) and β-olefinic protons (3·05 τ) gave the expected AB quartet ($J_{\alpha,\beta} = 10{\cdot}5$ c./sec.). However, each of the β-components was split further into a doublet ($J = 2$ c./sec.). The origin of this splitting was investigated by Dr. D. W. Turner by spin–spin decoupling.[2] Irradiation of the sample in the region of the band corresponding to the methine proton [asterisk in (III)] (multiplet at 5·28 τ) caused the



(I)



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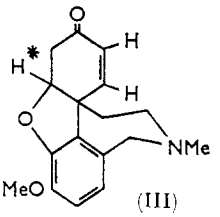

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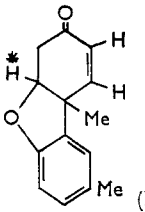

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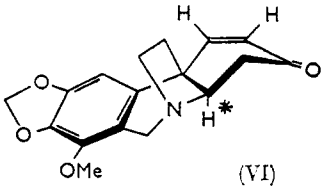
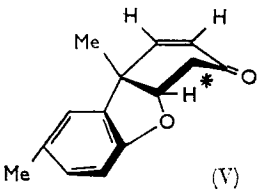


(VI)



(V)

β-proton doublets to collapse to singlets. Confirmation of this long-range coupling was obtained in the following way. It is known[3] that narwedine racemises in hydroxylic solvents. Opening of the benzofuran ring, with loss of a methylene proton, occurs in basic solution, the alkaloid itself being sufficiently basic to achieve this. The resulting symmetrical dienone can then reclose, to regenerate narwedine, the phenolic hydroxyl group adding to either double bond of the dienone ring. Consequently, the methylene protons α to the carbonyl group, *and* the α-olefinic proton are exchangeable in hydroxylic solvents. In agreement with this, recrystallisation of narwedine from deuteromethanol (MeOD) gave the trideutero-derivative lacking the α-proton band at 4·00 τ and also lacking doublets at 6·96 and 7·16 τ, ascribable to the methylene group. The β-(3·08 τ) and methine-proton bands (5·31 τ) now appeared as simple doublets ($J = 2$ c./sec.).

The same effect has been observed with the more accessible compound, Pummerer's ketone[4] (IV). Again, the olefinic protons gave an AB quartet (α, 4·12 τ; β, 3·58 τ; $J_{\alpha,\beta} = 10{\cdot}0$ c./sec.), with further splitting ($J = 2{\cdot}0$ c./sec.) of the β-proton bands. As in narwedine, the α-components showed no detectable fine splitting. The methine proton [asterisk in (IV)] appeared as a closely spaced sextet (5·35 τ) which could have arisen from splitting ($J \sim 3$ c./sec.) by the methylene group, to give a triplet or overlapping double-doublet which was split further ($J \sim 2$ c./sec.) by the β-olefinic proton. The methylene group gave a partially resolved multiplet (7·12 τ) whose general appearance was consistent with coupling of the two non-equivalent protons between themselves ($J = 17{\cdot}5$ c./sec.) and with the neighbouring methine proton ($J \sim 3$ and ~ 4 c./sec.). Equilibration of Pummerer's ketone with MeOD containing a trace of alkoxide gave the corresponding trideutero-ketone. The methine (5·38 τ) and β-olefinic (3·60 τ) bands were, as expected, doublets ($J = 2{\cdot}0$ c./sec.) although some broadening of the β-doublet, presumably caused by coupling with the α-deuterium, was observed.

The long-range coupling discussed here resembles in magnitude that observed between

[2] Turner, *J.*, 1962, 847.
[3] Barton and Kirby, *J.*, 1962, 806.
[4] Pummerer, Melamed, and Puttfarcken, *Ber.*, **1922**, **55**, 3116.

the C-2 and C-6 and the C-3 and C-5 protons of cyclohexa-2,5-dienones.[5] It is likely therefore that spin-coupling in these compounds is large when the relevant C–H bonds lie in, or nearly in, the plane containing the intervening carbon atoms. This is possible for narwedine and Pummerer's ketone if the aryl group is placed in a quasi-equatorial position (V). In contrast, the n.m.r. spectrum of powellinone (VI), described by Lloyd *et al.*,[6] shows a simple AB quartet for the olefinic protons. In agreement with these workers, we find no significant (<0·5 c./sec.) fine splitting of the olefinic signals. Lack of coupling is consistent with the conformation (VI) in which the methine proton [asterisk in (VI)] lies outside the median plane of the ring.

Note added in proof (*September 7th*, 1964): Rapoport and Sheldrick have observed (*J. Amer. Chem. Soc.*, 1963, **85**, 1636, footnote p. 1639) in " thebaine-hydroquinone " a long-range coupling ($J \sim 2$ c./sec.) which appears similar in type to the examples described here. The configuration assigned to this compound supports our stereochemical arguments.

Experimental.—All n.m.r. spectra were run on a Varian A60 spectrometer in deuterochloroform solution using tetramethylsilane as an internal standard. M. p.s were measured on a Kofler hot-stage apparatus.

Isomerisation of Galanthamine.—A solution of (−)-galanthamine (250 mg.) in 2% hydrochloric acid (20 ml.) was refluxed for 3 hr., cooled, treated with an excess of sodium hydrogen carbonate, and extracted with ether. The extract was evaporated and the residue chromatographed in benzene on alumina (grade V). Elution with benzene–ethyl acetate (3 : 1) gave (−)-epigalanthamine (160 mg.) as plates, m. p. 188—189° (from benzene), $[\alpha]_D$ −243° (*c* 1·02 in $CHCl_3$) (Found: C, 71·1; H, 7·3; N, 4·8%. Calc. for $C_{17}H_{21}NO_3$: C, 71·05; H, 7·4; N, 4·9%). Bubewa-Iwanowa [1] recorded m. p. 182—184°, $[\alpha]_D$ −220° (*c* 1 in $CHCl_3$) and Kondo, Ishiwata, and Okayama [7] (for the natural alkaloid), m. p. 190°, $[\alpha]_D$ −220° (in MeOH). Our specimen had an infrared spectrum in chloroform identical with that of (±)-epigalanthamine.[3]

Oxidation of (−)-Epigalanthamine.—Oxidation was carried out with manganese dioxide in chloroform in the usual way.[3] The crude product was chromatographed on alumina (grade V), elution with benzene–ethyl acetate (9 : 1) giving (±)-narwedine as needles, m. p. and mixed m. p. 189—190° (from ethanol). The infrared spectrum (Nujol) was identical with that of a specimen obtained by the oxidation of (−)-galanthamine in the same conditions.

(±)-*Trideuteronarwedine.*—A solution of (±)-narwedine (50 mg.) in MeOD [8] (2 ml.) was heated under reflux for 5 min., concentrated, and cooled. The trideutero-derivative which crystallised out was collected and dried at 50° *in vacuo*.

Deuteration of Pummerer's Ketone.—Oxidation of *p*-cresol was carried out with potassium ferricyanide.[4] The alkali-insoluble product was chromatographed on alumina (grade III) and the required ketone eluted with benzene. Pummerer's ketone crystallised from ethanol as needles, m. p. 124° (lit.,[4] 124°). Deuteration of the ketone (200 mg.) was effected within 5 min. in boiling MeOD [8] (2 ml.) containing potassium t-butoxide (5 mg.). The trideutero-derivative crystallised from the cooled solution and was collected and dried *in vacuo* at room temperature.

We thank Professor D. H. R. Barton, F.R.S., for encouragement, Dr. D. W. Turner for the spin decoupling experiment, Professor F. L. Warren and Dr. A. Goosen for a sample of powellinone, and Dr. L. Bubewa-Iwanowa for courteous exchange of information.

CHEMISTRY DEPARTMENT, IMPERIAL COLLEGE, LONDON S.W.7. [*Received, January 20th*, 1964.]

[5] Haynes, Stuart, Barton, and Kirby, *Proc. Chem. Soc.*, 1963, 280, and references therein cited.
[6] Lloyd, Kielar, Highet, Uyeo, Fales, and Wildman, *J. Org. Chem.*, 1962, **27**, 373.
[7] Kondo, Ishiwata, and Okayama, *J. Pharm. Soc. Japan*, 1933, **53**, 807.
[8] Hobden, Johnston, Weldon, and Wilson, *J.*, 1939, 61.

898. *Some Magnetic Properties of the Compound* $PCrCl_8$.

By D. J. Machin, D. F. C. Morris, and E. L. Short.

Thousands of complexes of chromium(III) have been prepared, and there do not appear to be any proved exceptions to the rule that chromium(III) has a co-ordination number of 6 in chemical combination.[1] This is in agreement with crystal-field theory, which indicates that the stabilization of high-spin regular octahedral complexes formed by ions of elements constituting the first half of the first transition series is a maximum when the ions possess the $[Ar]d^3$ electronic configuration.[2]

In this Note we present evidence for the possible existence of the tetrachlorochromate(III) ion with a distorted tetrahedral structure. This ion may exist in the blue compound $PCrCl_8$ which was first prepared by Weber [3] in 1859 and investigated by Cronander [4] in 1873.

Schöber and Gutmann [5] claimed to have identified $[CrCl_4]^-$ polarographically in solutions of chromium(III) chloride in dimethyl sulphoxide containing an excess of chloride ions. Schläfer and Opitz [6] also studied the system Cr^{3+}–Cl^- in dimethyl sulphoxide but do not report the formation of $[CrCl_4]^-$.

The Table contains results from magnetic susceptibility measurements made by the Gouy method on the compound $PCrCl_8$ over the temperature range 80—300°K. Measurements could not be made on the compound in solution because no medium has been found in which it is sufficiently soluble without reaction with the solvent.

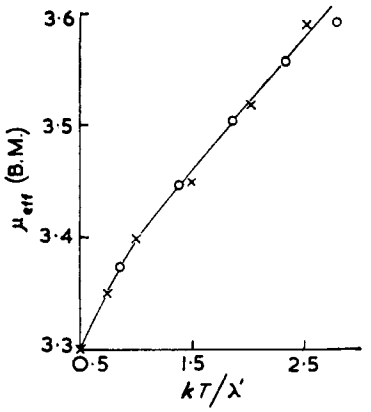
Magnetic measurements on $PCrCl_8$.

Experimental data				Calculated data for $A = 1{\cdot}32$, $v = 6$, $k = 0{\cdot}75$, $\lambda' = 73$ cm.$^{-1}$.	
Temp. (°K)	μ_{eff} (B.M.)	Temp. (°K)	μ_{eff} (B.M.)	kT/λ	μ_{eff} (B.M.)
303·2	3·59	163·8	3·46	2·5	3·59
279·5	3·59	141·8	3·45	2·0	3·52
256·3	3·58	119·9	3·41	1·5	3·45
232·4	3·55	110·4	3·40	1·0	3·40
208·3	3·50	99·5	3·37	0·75	3·35
186·5	3·50			0·50	3·30

The magnetic moment at room temperature, 3·6 B.M., is within the range expected for a chromium(III) complex; the fact that chromium in $PCrCl_8$ has the oxidation number +3 is also indicated by the formula of the compound. Our magnetic data are consistent with a formulation $[PCl_4]^+[CrCl_4]^-$, with ions of tetrahedral symmetry. The ground term of chromium(III) in a tetrahedral environment is $^4T_1$, and our experimental data have been compared with the results of calculations [7] of the magnetic behaviour of ions having this ground term. The variation of the effective magnetic moment, μ_{eff}, has been calculated as a function of the following four parameters: (i) kT/λ, where k is the Boltzmann constant, T is the absolute temperature, and λ is the spin–orbit coupling constant; (ii) A, a term which takes into account the mixing of the ^4F and ^4P states of the free cation; (iii) k, the orbital reduction factor, which is a measure of the extent of electron delocalisation from

[1] Cotton and Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, 1962.
[2] Orgel, "An Introduction to Transition-Metal Chemistry Ligand-Field Theory," Methuen, London, 1960.
[3] Weber, *Pogg. Ann.*, 1859, *B*, **107**, 375.
[4] Cronander, *Uppsala Univ. Årsskr.*, 1873.
[5] Schöber and Gutmann, Proc. Seventh Internat. Conf. Coordination Chem., 1962.
[6] Schläfer and Opitz, *Z. Chem.*, 1962, **6**/**7**, 216.
[7] Figgis, personal communication.

the metal ion to the ligands; the d electrons may be considered as spending $1 - k$ of their time on the ligands; (iv) v, a measure of the distortion of the ligand field from cubic symmetry. The calculations are similar to those previously made for $^2T_2$ terms.[8] It can be seen from the Figure that quite good agreement is obtained between experimentally determined values for μ_{eff} and calculated results when $A = 1{\cdot}32$, $k = 0{\cdot}75$, $v = 6$, and $\lambda' = 73$ cm.$^{-1}$, except for some deviation at the high temperatures. A distortion of the cubic ligand-field along a tetragonal or trigonal axis results in the splitting of the ^4T term into ^4A and ^4E components, and, if the separation between these is Δ', then $v = \Delta'/\lambda$. The value of $v = 6$ yields $\Delta' = 440$ cm.$^{-1}$, and, being positive, indicates that the ^4A term lies lowest. The spin–orbit coupling constant is reduced to 80% of the value for the free ion Cr^{3+}. The fairly low value of k is not surprising since delocalisation in a tetrahedral complex can occur by both σ- and π-mechanisms. It follows that the magnetic data are

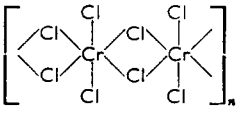


Plot of μ_{eff} against kT/λ.
○ Experimental results.
× Calculated results: $A = 1{\cdot}32$; $k = 0{\cdot}75$; $v = 6$ (*i.e.*, $\Delta' = 438$ cm.$^{-1}$); $\lambda'/\lambda = 0{\cdot}8$.

consistent with a distorted tetrahedral environment of chromium(III) in $PCrCl_8$. A distortion from regular tetrahedral symmetry is to be expected on the basis of the Jahn–Teller theorem.

The possibility that $PCrCl_8$ might contain a monomeric octahedral chromium(III) complex is ruled out since the $^4A_2$ ground term of such a species gives rise to a magnetic moment which is essentially independent of temperature.[9] Of possible polymeric octahedral species, the presence of a dimeric μ-trichloro-species is unlikely since the room-temperature value of μ_{eff} for tristetraethylammonium-μ-trichlorobis[trichlorochromate(III)] is 3·96 B.M.,[10] and it seems improbable that a change in cation would reduce the value to 3·6 B.M. The low value of μ_{eff} for $PCrCl_8$ compared with that for $[Et_4N]_3[Cr_2Cl_9]$ suggests that there would be a relatively strong antiferromagnetic interaction in the former compound if it were octahedral, although the values of the Weiss constants, θ, are small and approximately the same ($\sim$10°) in each case, and a plot of the reciprocal of the magnetic susceptibility against T is a straight line in the case of $PCrCl_8$. The compound $[Et_4N]_3[Cr_2Cl_9]$ deviates from a Curie–Weiss law at low temperatures.

A possible structure which cannot be completely ruled out for $PCrCl_8$ is a long-chain polymer consisting of octahedra sharing edges.



[8] Figgis, *Trans. Faraday Soc.*, 1961, **57**, 198, 204.
[9] Figgis, Lewis, and Mabbs, *J.*, 1961, 396.
[10] Earnshaw and Lewis, *J.*, 1961, 396.

Experimental.—The compound $PCrCl_8$ was prepared by a method similar to that employed by Weber and by Cronander. Reagent grade phosphorus pentachloride and chromyl chloride were used without further purification. The preparation was carried out in a thick-walled Pyrex tube. Chromyl chloride was introduced through the neck of the tube and covered with

$$CrO_2Cl_2 + 3PCl_5 = PCrCl_8 + 2POCl_3 + 3/2Cl_2$$

a 15% (by weight) excess of phosphorus pentachloride. The mixture was cooled to −80° in an acetone–solid carbon dioxide bath and the tube was sealed at *ca.* 3 mm. pressure, and heated for about 3 hr. in a Carius furnace at 140°; at intervals it was removed and shaken. The product, which appeared as a moist blue mass, was transferred, in an atmosphere of nitrogen, to a vacuum-distillation apparatus (CAUTION: owing to the liberation of chlorine during the reaction pressure is built up and care must be exercised in opening the tube). Chlorine, phosphorus oxychloride, and excess phosphorus pentachloride were distilled from the mixture at 40—45°/*ca.* 8 mm. into a small flask cooled to −80°. When the pressure had dropped to about 2 mm. the residue remaining in the distillation flask was a light blue dry powder (Found: Cl, 77·7; Cr, 14·0; P, 8·3. Calc. for $PCrCl_8$: Cl, 77·4; Cr, 14·2; P, 8·5%).

The magnetic susceptibility was measured with a Gouy apparatus described previously.[11]

We are grateful to Dr. B. N. Figgis for making the results of his calculations available to us prior to publication.

(D. J. M.) Department of Chemistry, The University, Manchester 13.
Department of Chemistry, Brunel College, London W.3. [*Received, January 14th*, 1964.]

[11] Figgis and Nyholm, *J.*, 1959, 331.

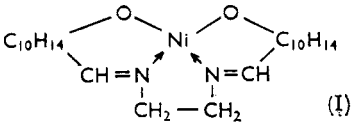
899. *The Magnetic Susceptibility of Bisformylcamphorethylenediaminenickel*(II) [NN′-*di*-(2-*hydroxyborn*-2-*en*-3-*ylmethylene*)*ethylenediaminatonickel*(II)] *in Solution.*

By R. S. Bluck, A. L. Odell, and R. W. Olliff.

Magnetically anomalous compounds of nickel(II) with Schiff base and oxime derivatives of salicylaldehyde have been the subject of many recent investigations.[1–6] Diamagnetic complexes of this class become paramagnetic when dissolved in organic solvents, and in most cases the apparent magnetic moments are intermediate between the spin-paired value ($\mu = 0$) and that typical of spin-free nickel(II) complexes ($\mu \sim 3{\cdot}1$ B.M.). Explanations

[1] Willis and Mellor, *J. Amer. Chem. Soc.*, 1947, **69**, 1237.
[2] Clark and Odell, *J.*, 1955, 3431.
[3] Sacconi, Paoletti, and Del Re, *J. Amer. Chem. Soc.*, 1957, **79**, 4062.
[4] Sacconi, Cini, Ciampolini, and Maggio, *J. Amer. Chem. Soc.*, 1960, **82**, 3487.
[5] Clark and O'Brien, *Canad. J. Chem.*, 1961, **39**, 1031; Clark, Macvicar, and O'Brien, *ibid.*, 1962 **40**, 822.
[6] Holm, Proc. Sixth Internat. Conference on Coordination Chemistry, MacMillan, New York, 1961, p. 341.

suggested for this phenomenon include square-tetrahedral isomerism,[1,2,7] solvent addition to form octahedra,[2,8] ligand-field distortion,[9,10] and reversible dimerisation.[5,11]



(I)

Bisformylcamphorethylenediaminenickel(II) [*NN'*-di-(2-hydroxyborn-2-en-3-ylmethylene)ethylenediaminatonickel(II)] (I) is usually included [12,13] in this family of anomalous nickel compounds having "intermediate" magnetic moments in solution, and was, in fact, the first reported [12] member of it.

Experimental.—Bisformylcamphorethylenediaminenickel(II) was prepared by the method of Pfeiffer and his co-workers.[14] These workers claimed that the complex [14] crystallises from aqueous n-propanol with three molecules of water of crystallisation. We have found that it crystallises from this solvent mixture as olive-green crystals with one molecule of n-propanol (product A) which is easily removed by heating for one hour at 100° to form product B with no solvent of crystallisation [(A) Found: C, 64·7; H, 8·45; N, 5·6; Ni, 11·9. Calc. for $C_{24}H_{34}O_2N_2Ni,C_3H_8O$: C, 64·7; H, 8·45%; N, 5·6; Ni, 11·7. (B) Found: C, 65·6; H, 7·6; Ni, 13·5; N, 6·3. Calc. for $C_{24}H_{34}O_2N_2Ni$: C, 65·3; H, 7·8; N, 6·35; Ni, 13·3%.]

Magnetic susceptibilities at 25° were determined on a Gouy-type magnetic balance which has already been described.[2] Absorption spectra were obtained on a Shimadzu model QR50 spectrophotometer.

Results and Discussion.—The magnetic susceptibility of bisformylcamphorethylenediaminenickel(II) in the solid state has been redetermined, and the complex found to be diamagnetic, as previously reported.[15]

Methanol solutions of the complex were found to be diamagnetic when freshly prepared, χ_g for the complex being $-0{\cdot}843 \times 10^{-6}$ c.g.s.u. This result is at variance with the observations of Lifschitz,[13] French *et al.*,[12] and Willis and Mellor,[1] who reported paramagnetic moments intermediate between zero and 3·1 B.M. [the value expected for spin-free nickel(II) complexes]; their values were 2·35, 1·9, and 1·4 B.M., respectively.

When the solution in methanol was stored in a tube closed with a rubber stopper, the susceptibility increased with time (see the Table). A sample of the methanol solution sealed in a glass tube remained diamagnetic for 14 days, the gram susceptibility of the complex changing from $-0{\cdot}949 \times 10^{-6}$ to $-0{\cdot}357 \times 10^{-6}$ c.g.s.u.

Time-dependence of the gram susceptibility of bisformylcamphorethylenediaminenickel(II) in methanol.

Time (days)	0	1	17	28	45	78
$\chi_g \times 10^6$ (c.g.s.u.)	−0·843	−0·475	+2·418	+2·948	+3·281	+3·440
μ (B.M.)	0·00	0·00	1·78	1·93	2·02	2·06

In order to determine which component of the atmosphere was responsible for the increase in magnetic susceptibility, four samples of a methanol solution of the complex were stored, under the conditions described below, for 10 days, and their susceptibilities then determined.

(*a*) Open to the air: $\chi_g = +3{\cdot}061 \times 10^{-6}$ c.g.s.u.
(*b*) Sealed: $\chi_g = -0{\cdot}564 \times 10^{-6}$ c.g.s.u.
(*c*) Sealed with a few drops of water: $\chi_g = -0{\cdot}598 \times 10^{-6}$ c.g.s.u.
(*d*) Sealed under oxygen gas at 40 p.s.i.: $\chi_g = +4{\cdot}606 \times 10^{-6}$ c.g.s.u.

[7] Sacconi, Orioli, Paoletti, and Ciampolini, *Proc. Chem. Soc.*, 1962, 255; Sacconi, Paoletti, and Ciampolini, *J. Amer. Chem. Soc.*, 1963, **85**, 411; Sacconi and Ciampolini, *ibid.*, p. 1750; Sacconi, *J.*, 1963, 4608.
[8] Basolo and Matoush, *J. Amer. Chem. Soc.*, 1953, **75**, 5663.
[9] Maki, *J. Chem. Phys.*, 1958, **28**, 651; 1959, **29**, 162, 1129.
[10] Ballhausen and Liehr, *J. Amer. Chem. Soc.*, 1959, **81**, 538.
[11] Holm and McKinney, *J. Amer. Chem. Soc.*, 1960, **82**, 5506.
[12] French, Magee, and Sheffield, *J. Amer. Chem. Soc.*, 1942, **64**, 1924.
[13] Lifschitz, *Rec. Trav. chim.*, 1947, **66**, 401.
[14] Pfeiffer, Christeleit, Hesse, Pfitzher, and Thielert, *J. prakt. Chem.*, 1938, **150**, 261.
[15] Mellor, *Proc. Roy. Soc. N.S.W.*, 1941, **75**, 157.

Solutions (*b*) and (*c*) remained dark green in colour throughout, whereas (*a*) and (*d*) changed to brown-green, (*d*) also depositing a pale yellow precipitate.

Hydrogen gas was subsequently bubbled through solution (*a*), in order to determine whether the changes accompanying oxygen absorption were reversible. After several days, however, the brown-green colour was unchanged. The oxygen absorption is thus irreversible.

The increase in magnetic susceptibility was accompanied by changes in the absorption spectrum. The intensity of the peak at 390 mμ (usually associated [7,16] with square-planar nickel(II) complexes) decreased steadily as oxygen was absorbed, as did that at 240 mμ. The peak at 290 mμ increased in intensity.

Similar results were observed for benzene solutions.

Increasing the pressure of oxygen accelerated the changes in the magnetic susceptibility and in the spectra, and accelerated the appearance of the yellow precipitate. On a large scale, 1·2135 g. of the complex was dissolved in 100 ml. of methanol and oxygenated, with shaking, in a Parr hydrogenation apparatus at 58 p.s.i. of oxygen. The solution slowly turned brown, and then slowly deposited a yellow precipitate. After 36 hours, the complex in the non-filtered mixture gave $\chi_g = 8{\cdot}765 \times 10^{-6}$ c.g.s.u. (after allowing the dissolved oxygen to equilibrate with the air), corresponding to 3·15 B.M. The fact that this value corresponds to the " spin-free " value for nickel(II) complexes, coupled with the observation that absorption peaks at 240 and 390 mμ had entirely disappeared, was taken as evidence that the oxygenation reaction had gone to completion.

The yellow precipitate was isolated and gave $\chi_g = +14{\cdot}45 \times 10^{-6}$ c.g.s.u. (Found: C, 37·7; H, 6·4; N, 4·05; Ni, 21·9%); its magnetic moment is thus calculated (after allowing a diamagnetic correction of 250×10^{-6} c.g.s.u.) to be 3·15 B.M. It was insoluble in most organic solvents, but showed slight solubility in methanol; it could not be recrystallised. The empirical formula indicated by the above analysis is approximately $C_{8{\cdot}4}H_{17{\cdot}08}N_{0{\cdot}77}O_{5{\cdot}0}Ni$.

Although the sample is obviously impure, it is clear that there has been extensive decomposition of the starting material, $C_{24}H_{34}N_2NiO_2$. The nature of the oxidation product has not been established, but it is clear that the high magnetic susceptibilities previously reported for solutions of bisformylcamphorethylenediaminenickel(II) in organic solvents are due to extensive oxidative decomposition of the ligand.

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Chemistry Department, University of Auckland,
Auckland, New Zealand. [*Received, December 30th*, 1963.]

[16] Clark and Odell, *J.*, 1956, 520.

900. *Kinetics of Nucleophilic Substitution in Polyfluoroaromatic Compounds. The Reaction of Sodium Methoxide with Hexafluorobenzene.*

By J. Burdon, W. B. Hollyhead, and C. R. Patrick.

In contrast to the nucleophilic displacement of halogen atoms from lightly halogenated aromatic compounds, the displacement of fluorine from the aromatic nuclei of highly fluorinated compounds often proceeds easily, and is involved in several useful synthetic reactions. This difference in behaviour has been attributed to the combined inductive effect of the substituent fluorine atoms. Previous Papers [1] have dealt qualitatively with the directing effects of other substituents on nucleophilic reactions with highly fluorinated benzenes. We now describe a quantitative study of a simple example, the reaction of sodium methoxide in methanol with hexafluorobenzene.

Experimental.—Hexafluorobenzene was shown by gas chromatography to be pure.

In kinetic experiments equal concentrations of the two reactants were used. Hexafluorobenzene was weighed into a flask, and to this was pipetted the required volume of sodium methoxide in methanol whose concentration was determined immediately before use by titration with hydrochloric acid. The mixtures were adjusted to the desired concentrations (0·35—0·45 mole $l.^{-1}$) by dilution with dry methanol. Aliquot parts (2 ml.) of the stock solutions of reaction mixtures were pipetted rapidly after preparation into sample tubes which were kept for 15 min. in " Drikold "–ethanol to allow the contents to drain to the bottoms. The tubes were then sealed and transferred to a water thermostat (±0·05°). At subsequent intervals tubes were removed, cooled rapidly in " Drikold "–ethanol, opened, and their contents analysed by gas chromatography on silicone gum in a Perkin-Elmer gas Fraktometer with a hot-wire detector. A weighed portion of an inert substance, *p*-xylene, was added to the reaction mixture and a sample of the resultant mixture was injected into the column, which was operated under standardised conditions.

The heights of the peaks recorded for the eluted bands of *p*-xylene and pentafluoroanisole were measured. The amounts of pentafluoroanisole were determined from the ratio of these heights and comparison with calibration curves from standards (made in solutions of sodium methoxide in methanol).

In no experiment was tetrafluorodimethoxybenzene observed in gas chromatograms, nor was any precipitate (such as sodium fluoride) formed in the reaction systems.

Results.—Rates measured at 40—60° all obeyed a second-order kinetic expression. Reaction was allowed to proceed to at least 60%, sometimes 80%, completion. The results are tabulated (k in l. $mole^{-1}$ $sec.^{-1}$).

10^4k	1·96	1·96	1·96	2·13	3·02	4·11	4·10
Temp.	44·3°	45·5°	45·5°	45·5°	46·9°	49·0°	49·0°
10^4k	5·50	5·56	8·20	8·90	10·3	13·0	13·0
Temp.	52·0°	52·0°	55·5°	56·0°	57·3°	59·5°	59·5°

The Arrhenius plot for the second-order rate coefficient was linear and was fitted by the least-square treatment to represent the equation:

$$k = 10^{14\cdot3\pm0\cdot4} \exp -[26\cdot1 \pm 0\cdot7 \text{ (kcal)}/RT] \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

The limits represent the standard deviations of the quantities.

Discussion

In its obedience to second-order kinetics this reaction behaves as do other reactions of the same type such as the displacement of halide ions from halogenonitrobenzenes by

[1] Tatlow, *Endeavour*, 1963, **22**, 89, and references therein.

alkoxide ions and aniline [2-5] and appears to proceed by the S_N2 mechanism. It is particularly relevant to compare the present results with those for the reaction of sodium methoxide with fluorobenzene, for which [4,5] the bimolecular rate coefficient can be described by:

$$k = 10^{12.5 \pm 0.5} \exp -[35.6 \pm 1.0 \text{ kcal.}/RT] \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

The ratio of the rate coefficient for the reaction with hexafluorobenzene at 50° to that for fluorobenzene (about 4×10^{-11} l. mole^{-1} sec.$^{-1}$) is about 10^7. To this factor the greater contribution is due to the difference between the energies of activation for the two reactions, although a factor of somewhat more than 10, but less than 100, is due to the different values of the pre-exponential factors. This is as expected, since it is implicit in most electronic interpretations of differences between the reactivity of aromatic compounds towards a common nucleophile that such differences should be associated with the energies of activation. In studies [2,3] of nucleophilic substitution of halogeno-nitrobenzenes lower values of pre-exponential factors have been observed, but not explained. Differences between pre-exponential factors are more difficult to explain but are probably associated with solvation effects, in which case they are likely also to be associated with changes in energies of activation that are not due directly to electronic effects as normally understood.

We thank the D.S.I.R. for a grant (to W. B. H.) and Professor J. C. Tatlow for his interest.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM 15. [*Received, December 12th*, 1963.]

[2] Heppolette, Miller, and Williams, *J.*, 1955, 2929.
[3] Parker and Reed, *J.*, 1962, 3149.
[4] Bevan and Bye, *J.*, 1954, 3091.
[5] Bolto, Leveris, and Miller, *J.*, 1956, 750.

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901. *The Mixed Hydrogen Dihalide Anions* $HBrCl^-$ *and* $HClI^-$.

By J. A. SALTHOUSE and T. C. WADDINGTON.

THE HF_2^- anion has been known for many years,[1] although its detailed structure has been elucidated only comparatively recently.[2] In the last few years, salts of the analogous anions HCl_2^-,[3] HBr_2^-,[4] and HI_2^- [5] have been prepared, and infrared spectra [3] and crystal entropy measurements [6] have been used to deduce that the HCl_2^- ion is symmetrical. We have now prepared crystalline samples of salts containing the mixed hydrogen dihalide anions $HBrCl^-$ and $HClI^-$. Infrared-spectral data for these anions, together with those of the HX_2^- species, are shown in the Table.

Experimental.—Tetra-n-butylammonium hydrogen bromide chloride. An excess of hydrogen bromide was added to a solution of tetra-n-butylammonium chloride in liquid hydrogen chloride at −96°, and the mixture equilibrated for *ca.* 15 min. The solvent was distilled off at −78°, leaving a colourless solid, $Bu^n_4N^+ Br(HCl)_2^-$; on warming to room temperature, it melted to a pale yellow liquid which, on careful pumping at 0°, gave *tetra-n-butylammonium hydrogen bromide chloride*, $Bu^n_4N^+ HBrCl^-$, a colourless solid (Found: C, 53·2; H, 10·1; Br,

[1] Bozorth, *J. Amer. Chem. Soc.*, 1923, **45**, 2128.
[2] Coté and Thompson, *Proc. Roy. Soc.*, 1951, *A*, **210**, 206.
[3] Waddington, *J.*, 1958, 1708.
[4] (*a*) Tuck and Woodhouse, *Proc. Chem. Soc.*, 1963, 53; (*b*) Waddington and White, *J.*, 1963, 2701.
[5] McDaniel and Vallée, *Inorg. Chem.*, 1963, **2**, 997.
[6] Chang and Westrum, *J. Chem. Phys.*, 1962, **36**, 2571.

Characteristic infrared frequencies for hydrogen dihalide anions.

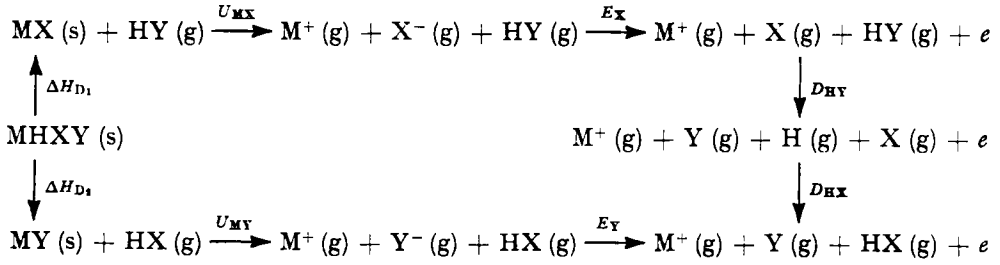
Anion	ν_3 (cm.$^{-1}$) (Asym. stretch)	ν_2 (cm.$^{-1}$) (Bend)		Ref.
HF_2^-	1450	1223	KHF_2	2
HCl_2^-	1565	1180	Me_4NHCl_2	3
	1565	1160	Me_4NHCl_2	5
	1540	1150	$Bu^n_4NHCl_2$	5
	1625	1150	$Si(acac)_2CHCl_2$	5
HBr_2^-	1700		Et_4NHBr_2	4 (*a*)
	1670	1170	Et_4NHBr_2	5
	1690	1170	$Bu^n_4NHBr_2$	5
HI_2^-	1650	1165	$Bu^n_4NHI_2$	5
$HBrCl^-$	1650	1100	$Bu^n_4NHBrCl$	
$HClI^-$	2000	990	Bu^n_4NHClI	

21·5; Cl, 9·7. $C_{16}H_{37}BrClN$ requires C, 53·5; H, 10·0; Br, 22·2; Cl, 9·9%). The halide analyses were performed potentiometrically, and the total halide content was checked gravimetrically. In two separate estimations, 1 mole of the compound liberated 0·99 mole of acid; the required amount is 1·0 mole of acid. Heating of this compound, followed by pumping, led to the formation of tetra-n-butylammonium bromide.

Tetra-n-butylammonium hydrogen chloride iodide. In a similar manner, a solution of tetra-n-butylammonium iodide in liquid hydrogen chloride was prepared, and the solvent was evaporated at −78°, leaving a pale yellow solid, $Bu^n_4N^+ I(HCl)_2^-$; on warming to room temperature, this melted to a pale yellow liquid which, on pumping at 0°, gave tetra-n-butylammonium hydrogen chloride iodide, $Bu^n_4N^+ HClI^-$, a pale yellow solid, v. p. *ca.* 8 mm. at 0° (Found: Cl, 9·1; I, 31·2. $C_{16}H_{37}ClIN$ requires Cl, 8·8; I, 31·4%. 1 mole of the compound liberated 1·09 mole of acid; the required amount is 1·0 mole of acid.) On heating and pumping of the compound, hydrogen chloride was removed and tetra-n-butylammonium iodide remained.

A solution of tetra-n-butylammonium iodide in liquid hydrogen bromide was prepared, and the solvent was evaporated at −78°, leaving a solid, $Bu^n_4N^+ I(HBr)_2^-$; on warming to room temperature, this gave a liquid which, on careful pumping at 0°, gave tetra-n-butylammonium hydrogen dibromide $Bu^n_4N^+ HBr_2^-$. On heating and pumping of this compound, hydrogen bromide was removed and tetra-n-butylammonium bromide remained. The compounds were rather unstable at room temperature and fumed in moist air; the hydrogen bromide chloride was very deliquescent, but the hydrogen chloride iodide was not exceptionally so. In the salts, the low-frequency infrared vibrations of the anions (1000—1200 cm.$^{-1}$) tended to be masked by the infrared vibrations of the tetra-n-butylammonium cation.

Discussion.—The mode of decomposition of these mixed hydrogen dihalides is of interest; it is completely different from that of a mixed polyhalide such as $MICl_2$, which decomposes to give MCl and ICl rather than MI and Cl_2.



From the above, we have

$$\Delta H_{D1} - \Delta H_{D2} = (U_{MY} - U_{MX}) + (E_Y - E_X) - (D_{HY} - D_{HX}) = \Delta U + \Delta E_A - \Delta(D_{HX})$$

where ΔU is the difference in lattice energies of the two simple halides, ΔE_A is the difference in their electron affinities, and $\Delta(D_{HX})$ is the difference in the dissociation energies of the

hydrogen halides. For $HBrCl^-$, ΔE_A is 6 kcal. mole^{-1} and $\Delta(D_{HX})$ is -16 kcal. mole^{-1}. Thus, if $\Delta U < 10$ kcal. mole^{-1} the bromide should result, ignoring entropy changes. In fact, even for the cæsium salts ΔU is only 6 kcal. mole^{-1}, so one would expect the bromide from all tetra-alkyl ammonium salts. Similarly for $HClI^-$, if ΔU is less than 23 kcal. mole^{-1} then the tetra-alkyl ammonium iodide should be produced. In fact, even for the cæsium salts ΔU is only 13 kcal. mole^{-1}.

Thus we see that in the polyhalides it is the lattice energy of the simple halide produced which determines the course of the reaction, whereas in the hydrogen dihalides it is the strength of the bond in the HX molecule produced.

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902. *Anthranilamides as Intermediates for 3-Substituted Quinazoline-2,4-diones.*

By Shreekrishna M. Gadekar, Anna Marie Kotsen, and Elliott Cohen.

According to Taub and Hino [1] one of the disadvantages in the synthesis of 3-substituted quinazoline-2,4-diones by Staiger and Wagner [2] is the formation of varying amounts of *N*-substituted anthranilamides. We now wish to report that the anthranilamides (Table 1) can be used advantageously as convenient intermediates for the preparation of these compounds.

Table 1.

Anthranilamides (I).

R	R′	Yield (%)	M. p.	Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
CH_2–CH=CH_2 *	Cl	78	122—125°	$C_{10}H_{11}ClN_2O$	57·0	5·26	13·3	56·8	5·34	13·4
$(CH_2)_2$·NMe_2 ...	H	82	139—141	$C_{11}H_{17}N_3O$,2HCl	47·2	6·84	15·0	47·2	6·99	15·0
$(CH_2)_3$·NMe_2 ...	H	67	219—221	$C_{12}H_{19}N_3O$,2HCl	49·0	6·85	14·3	49·3	7·22	14·0
$(CH_2)_3$·NMe_2 ...	Cl	64	82·5—83·5	$C_{12}H_{18}ClN_3O$	56·4	7·10	16·4	56·1	6·69	16·1
3-CH_2·C_5H_5N ...	H	70	127—128	$C_{13}H_{13}N_3O$	68·7	5·73	18·5	68·4	5·63	18·6
3-CH_2·C_5H_5N ...	Cl	69	141—142	$C_{13}H_{12}ClN_3O$	59·6	4·63	16·1	59·2	4·71	16·3
2-C_5H_5N	H	43	217—220	$C_{12}H_{11}N_3O$,2HCl	50·3	4·55	14·7	50·5	4·85	14·5
CMe_3	H	18	126—127	$C_{11}H_{16}N_2O$	68·7	8·39	14·6	68·7	8·42	14·3

* This compound was prepared first by Miss G. E. Wiegand in our laboratories.

The present method comprises heating an *N*-substituted anthranilamide (I) with ethyl chlorocarbonate to give a 2-carbethoxyaminobenzamide derivative (II) which is then cyclized under basic conditions to a quinazolinedione (III). The use of ethyl chlorocarbonate in these syntheses is not novel, for Sheibley [3] has reported the cyclization of 3,5-dihaloanthranilamides to the corresponding quinazolinediones with this reagent. The difference, however, is that the *N*-substituted anthranilamides when caused to react in

[1] Taub and Hino, *J. Org. Chem.*, 1961, **26**, 5238.
[2] Staiger and Wagner, *J. Org. Chem.*, 1953, **18**, 1427.
[3] Sheibley, *J. Org. Chem.*, 1947, **12**, 743.

TABLE 2.

2-Carbethoxyaminobenzamides (II).

R	R′	Yield (%)	M. p.	Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
Et *	H	69	100—101°	$C_{12}H_{16}N_2O_3$	61·0	6·83	11·9	61·3	6·96	12·2
CH_2–CH=CH_2...	Cl	73	112—113	$C_{13}H_{15}ClN_2O_3$	55·2	5·35	9·91	55·3	5·42	10·1
CH_2·CH_2·OH †	H	42	104—107	$C_{12}H_{16}N_2O_4$	57·1	6·39	11·1	57·1	6·27	10·9
$(CH_2)_2$·NMe_2 ...	H	81	147—150	$C_{14}H_{21}N_3O_3$,HCl	53·0	7·03	13·3	53·2	7·12	13·4
$(CH_2)_3$·NMe_2 ...	H	96	182—183	$C_{15}H_{23}N_3O_3$,HCl	54·6	7·34	12·7	54·9	7·51	13·0
$(CH_2)_3$·NMe_2 ...	Cl	90	199—200	$C_{15}H_{22}ClN_3O_3$,HCl	49·5	6·36	11·5	49·8	6·57	11·4
3-CH_2·C_5H_5N ...	H	83	195—196	$C_{16}H_{17}N_3O_3$,HCl	57·3	5·36	12·5	57·5	5·49	12·9
3-CH_2·C_5H_5N ...	Cl	82	222—223	$C_{16}H_{16}ClN_3O_3$,HCl	52·0	4·59	11·4	52·3	4·58	11·3
2-C_5H_5N	H	56	132—133	$C_{15}H_{15}N_3O_3$	63·2	5·30	14·7	63·0	5·42	14·0
CMe_3	H	92	161—163	$C_{14}H_{20}N_2O_3$	63·6	7·63	10·6	63·6	7·67	10·2

The corresponding anthranilamides have been reported by * Finger, *J. Prakt. Chem.*, 1888 (2), **37**, 431; † Shridhar and K. Narang, *J. Indian Chem. Soc.*, 1956, **33**, 308.

TABLE 3.

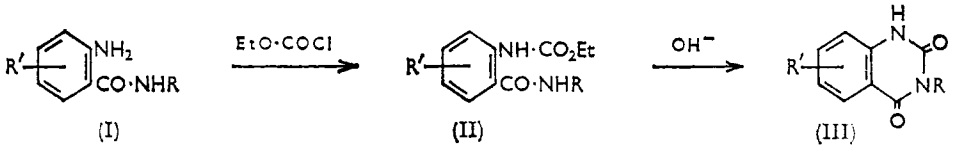
2,4-Quinazolinediones (III).

R	R′	Yield (%)	M. p.	Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
Et	H	89	196—198° *							
CH_2–CH=CH_2	Cl	91	234—235	$C_{11}H_9ClN_2O_2$	55·8	3·83	11·8	55·7	3·89	11·7
CH_2·CH_2·OH	H	21	246—249	$C_{10}H_{10}N_2O_3$	58·2	4·89	13·6	58·4	5·12	13·9
$(CH_2)_2$·NMe_2 ...	H	84	219—221	$C_{12}H_{15}N_3O_2$,HCl	53·4	5·98	15·6	53·6	5·97	15·3
$(CH_2)_3$·NMe_2 ...	H	73	180—182	$C_{13}H_{17}N_3O_2$,HCl	55·0	6·39	14·8	54·7	6·73	14·8
$(CH_2)_3$·NMe_2 ...	Cl	76	172—173	$C_{13}H_{16}ClN_3O_2$	55·4	5·73	14·9	55·7	5·92	15·2
3-CH_2·C_5H_5N...	H	92	236—237	$C_{14}H_{11}N_3O_2$	66·4	4·35	16·6	66·2	4·51	16·6
3-CH_2·C_5H_5N...	Cl	91	289—290	$C_{14}H_{10}ClN_3O_2$	58·4	3·48	14·6	58·2	3·72	14·8
2-C_5H_5N.....	H	71	253—255	$C_{13}H_9N_3O_2$,$\frac{1}{4}H_2O$	64·1	3·80	17·2	64·2	3·93	17·4
CMe_3	H	55	198—199	$C_{12}H_{14}N_2O_2$	66·0	6·47	12·8	66·1	6·44	12·7

* Reported m. p. 196°; Spring and Woods, *J.*, 1945, 625.

this manner, did not cyclize, but formed 2-carbethoxyaminobenzamides (Table 2). These were converted to the diones (Table 3) with refluxing ethanolic potassium hydroxide.

The cyclization of t-butylureamidobenzoic acid to the corresponding 3-substituted



(I) (II) (III)

quinazolinedione has been reported [2] to give benzoyleneurea with the loss of the t-butyl group. The preparation of 3-t-butyl-2,4-quinazolinedione from the carbethoxybenzamide was accomplished without difficulty by the present method.

EXPERIMENTAL

Experimental.—Anthranilamides (I). The anthranilamides in Table 1 were prepared essentially by the methods of Clark and Wagner.[4]

2-Carbethoxyaminobenzamides (II). *Procedure* (cf. Table 2). A mixture containing (0·005 mole) of an anthranilamide and 15 ml. of ethyl chlorocarbonate was heated over steam for 3 hr. The reaction mixture was evaporated *in vacuo* to a residue which was recrystallized from a

[4] Clark and Wagner, *J. Org. Chem.*, 1944, **9**, 55.

suitable solvent such as heptane or ethanol. The anthranilamides containing dialkyl aminoalkyl or pyridylmethyl moieties separated from the reaction mixtures as hydrochlorides on cooling and were recrystallized as such.

3-*Substituted quinazoline*-2,4-*diones* (III). *Procedure* (cf. Table 3). A mixture of (0·03 mole) of 2-carbethoxyaminobenzamide and 3·37 g. (0·060 mole) of potassium hydroxide in 150 ml. of ethanol was refluxed over steam for 4 hr. The reaction mixture was evaporated to dryness and the solution of the residue in a minimum amount of water was adjusted to pH 7—8 with acetic acid. The precipitated product was recrystallized from either ethanol or a mixture of ethanol and water. The diones containing the basic functional groups were isolated as their hydrochlorides and were recrystallized from alcohol or a mixture of alcohol and ether.

Microanalyses were performed by Mr. L. M. Brancone and his associates.

Organic Chemical Research Section, Lederle Laboratories Division,
American Cyanamid Company,
Pearl River, New York.

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