NOTES.

744. *Extractives from the New Zealand Myrtaceae. Part III.* Triterpene Acids from the Bark of* Leptospermum scoparium.

By R. E. CORBETT and M. A. MCDOWALL.

TRITERPENE acids have been reported from the bark and heartwood of a number of members of the family Myrtaceae.[1,2] The genus *Leptospermum* is represented in New Zealand by *L. ericoides* (A. Rich), *L. sinclarii*, and *L. scoparium*; the last is the most abundant and widely distributed native tree in New Zealand.

Extraction of the finely powdered outer bark with hexane yielded an amorphous mixture of acids. Fractionation by solvents failed to yield crystalline material, but chromatography on silica gel [3] gave crystalline betulic acid, oleanolic acid, and ursolic acid acetate. Silica gel is an excellent medium for the chromatographic separation of triterpene acids. This appears to be the first reported occurrence of ursolic acid acetate in Nature. Oleanolic acid acetate has been isolated from *Eucalyptus calophylla* bark.[1]

Experimental.—M. p.s are corrected. The silica gel used for chromatography was supplied by the Mallinckrodt Chemical Works, U.S.A. Infrared spectra were determined on a Perkin–Elmer spectrometer model 12C, in Nujol.

Extraction. The fibrous outer bark of *L. scoparium* was stripped from a tree growing near Dunedin, cut into short lengths, and ground to a fine powder (1·0 kg.). It was extracted (Soxhlet) for 48 hr. with hexane (4 l.), the extract was concentrated, the concentrate treated with 20% sodium hydroxide (3 × 200 c.c.), and the insoluble sodium salt (30 g.) dried, dissolved in methanol (800 c.c.) (charcoal), and acidified with concentrated hydrochloric acid (150 c.c.). The precipitated amorphous acid (21 g.) had m. p. 185—200°. Crystallization could not be

* Parts I and II, *J. Sci. Food Agric.*, 1953, **11**, 508, and *J.*, 1954, 1179, respectively.

[1] White *et al.*, *J.*, 1949, 3433; 1952, 5040.
[2] Arthur and Hui, *J.*, 1954, 1403.
[3] Barton and de Mayo, *J.*, 1954, 887.

effected. Further extraction of the bark with ether, and separation of the acidic material as described, gave more amorphous acid (7 g.). The infrared spectrum of this material was identical with that from the hexane extraction. Neutral compounds from the hexane extract (17 g.) and from the ether extract (15 g.) will be the subject of a future communication.

The acid (14 g.) from the hexane extract, in benzene–ether (9 : 1; 700 c.c.), was introduced on to a column of silica gel (900 g.) made up in hexane. The chromatogram was developed at a pressure of 5 cm. with benzene–ether (19 : 1), and ursolic acid acetate (7·9 g.) was eluted with this solvent (4·3 l.). From the same chromatogram, benzene–ether (10 : 1; 3·3 l.) eluted betulic acid (2·5 g.), closely followed by oleanolic acid (0·77 g.), eluted by the same solvent (2·3 l.).

Ursolic acid acetate, purified by repeated crystallization from 90% aqueous ethanol, had m. p. 285°, $[\alpha]_D^{20}$ +71·5° (*c* 1·9 in chloroform) (Found: C, 77·05; H, 10·3. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%). It formed methyl ursolate acetate, m. p. and mixed m. p. 248—248·5°, and ursolic acid, m. p. and mixed m. p. 295°.

Betulic acid (crystallized from ethanol) had m. p. and mixed m. p. 314°, $[\alpha]_D^{20}$ +5·7° (*c* 1·86 in pyridine). The m. p.s of methyl betulate, 226°, betulic acid acetate, 290°, and methyl betulate acetate, 203—204°, were all undepressed by appropriate authentic derivatives of betulic acid.

Oleanolic acid (recrystallized from ethanol) had m. p. 295—297°, $[\alpha]_D^{20}$ +69° (*c* 0·74 in chloroform), mixed m. p. 300—302° with an authentic specimen, m. p. 305°. It was converted into oleanic acid acetate, m. p. 256°, mixed m. p. 257° with an authentic specimen, m. p. 263°.

One of us (R. E. C.) thanks Professor Sir Alexander Todd, F.R.S., for facilities in his laboratory, and the Nuffield Foundation for a travel grant. We are indebted to Dr. D. E. White of the University of Western Australia for the authentic specimens of the three acids and their derivatives. This work has also been assisted by grants from the Research Fund of the University of New Zealand and from the Mellor Research Fund. Analyses are by Dr. A. D. Campbell of this Department.

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745. *The Fluorescence of Acridine and Acridone Solutions.*

By E. J. BOWEN and J. SAHU.

IT is often stated that acridine is highly fluorescent in alcoholic solution. This fluorescence is, in fact, due almost entirely to the water-content of the alcohol, and the substance is non-fluorescent in most organic liquids; it fluoresces strongly in water. The intensity of fluorescence at different temperatures for mixed solvents of water and alcohols has been studied. The fluorescence intensities diminished with rise of temperature, and the fall increased from the alcohol-rich to the water-rich mixtures. All the results could be empirically represented by $(1/F) - K = k \exp(-E/RT)$, where F is the absolute quantum yield of fluorescence, E an "activation energy of fluorescence quenching" (cal./mole), T the absolute temperature and K and k constants. The results are summarised in the Table.

The values of E are probably correct to $\pm 5\%$, but since K and particularly k depend very much on the choice of E their absolute accuracy is much less.

It is concluded that a hydroxylic environment tends to hold the excited acridine molecule in a rigid form where it has difficulty in losing energy by non-radiational processes.

Solutions of acridone in organic solvents are more fluorescent than those of acridine. In methyl, ethyl, and *iso*propyl alcohols, and in water, over the temperature range −70° to +20°, the quantum yields of fluorescence are practically unity. Solutions in acetone and in ethyl acetate have lower, temperature-dependent, yields and their constants are also given in the Table.

The above expression for the variation of fluorescence yield with temperature follows from the assumption of a temperature-independent radiation process competing with two energy-degradation processes, one temperature-independent and characterised by K

being greater than unity, and the other having a rate constant proportional to $e^{-E/RT}$. The significance of the energy of activation E is not easy to assess, but a consistent scheme seems to be as follows. The excited states of these molecules readily degrade their electronic energies by bending or twisting vibratory movements unless they are bound by inter-

Solutions of acridine in aqueous methanol, ethanol, and glycerol, and of acridone in acetone and ethyl acetate.

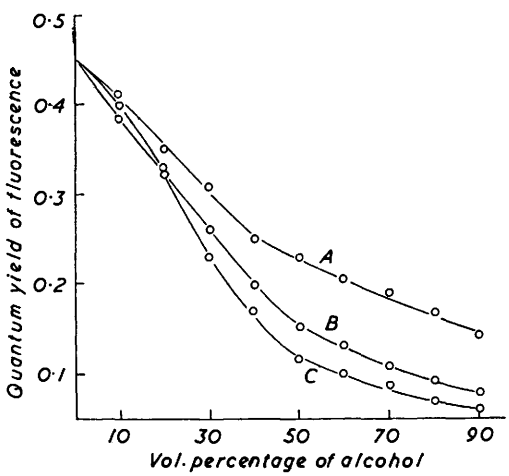
Alcohol (%, v/v)	K	$10^{-3}k$	E	Temp. range
		Methanol		
0 *	1	6·1	5000	20° to 70°
10	1·03	7·3	4950	20 to 60
20	1·1	8·8	4950	20 to 60
30	1·2	11	4900	20 to 50
40	1·7	13·4	4900	−20 to 20
50	2·0	16·4	4850	−30 to 20
60	2·4	20	4850	−50 to 20
70	3·1	24	4800	−50 to 20
80	3·5	30	4800	−50 to 20
90	5·0	35	4750	−50 to 20
		Glycerol		
10	1	7	5000	20 to 70
20	1	9·2	5000	20 to 70
30	1·4	9·2	5000	20 to 70
40	2	10	5000	20 to 70
50	2	14·2	5100	20 to 70
60	2	20·2	5200	20 to 70
70	2·7	25·4	5300	20 to 70
80	2·8	31·8	5400	20 to 70
90	4·0	37·4	5500	20 to 70

K	$10^{-3}k$	E	Temp. range
	Ethanol		
1	7·9	5000	20° to 60°
1·1	10·5	5000	20 to 60
1·4	15	5000	10 to 50
1·95	20	5000	−10 to 40
3·0	25	5000	−30 to 20
3·4	32	5000	−30 to 20
3·65	40	5000	−50 to 20
4·0	48	5000	−50 to 20
5·5	56	5000	−50 to 20
	Acridone in acetone		
1·0	5·2	4520	−50 to 20
	Acridone in ethyl acetate		
1·0	21	4520	−50 to 20

* *I.e.*, pure water.

molecular forces to solvent molecules. Such binding, assisted by high solvent viscosity (as in glycerol solutions), appears to limit the amplitudes of vibratory movements, and to make activation energy necessary for electronic energy degradation to occur.

Experimental.—Fluorescence intensities of solutions were measured in an apparatus already described,[1] which was designed to minimise errors due to refractive-index changes and other



Fluorescence intensity of water–alcohol solutions of acridine at 20°.

Fluorescence intensity of acridine in aqueous solutions of A, glycerol; B, methanol; C, ethanol.

complicating effects. The solution, at a concentration giving practically total light absorption, was illuminated in a tube at the centre of a whitened and evacuated spherical flask which acted as an integrating sphere and a Dewar vessel, and the fluorescence was collected from

[1] Bowen and Sahu, *J. Phys. Chem.*, 1958, in the press.

part of the flask wall by a calibrated photomultiplier–spectrograph combination. Using solutions of known absolute yield [2] we could obtain the fluorescence yields of the solutions by comparison of properly corrected fluorescence-band areas. Results for acridine in mixtures of water with methyl and ethyl alcohols and with glycerol at 20° are shown in the Figure. Dissolved air had only a small effect on the fluorescence. Measurements were also made of these solutions over such parts of the temperature range −50° to +60° as freezing points or high vapour pressures allowed.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, November 26th*, 1957.]

[2] Weber and Teale, *Trans. Faraday Soc.*, 1957, **53**, 646.

746. *Tracer Studies in Ester Hydrolysis. Part VII.* The Hydrolysis of 9-Fluorenyl Acetate.*

By C. A. BUNTON, G. ISRAEL, M. M. MHALA, and D. L. H. WILLIAMS.

IN Part IV of this series [1] results were reported of a mechanistic study of the hydrolysis of diphenylmethyl formate in acid, alkaline, and initially neutral solution, and of diphenylmethyl acetate in acid solution. This communication describes a study of the hydrolysis of the structurally similar 9-fluorenyl acetate, and an extension of the earlier work to the alkaline hydrolysis of diphenylmethyl acetate. The kinetic effect of the substitution of deuterium for protium on the alkyl-carbon atom of these esters has also been examined.

The S_N1 reactivity of an alkyl halide often indicates qualitatively the ease of alkyl–oxygen bond fission in the corresponding carboxylic ester. It has recently been suggested, on the basis of kinetic solvent effects and the variation of the Arrhenius parameters for the acid hydrolyses of various carboxylic esters of diphenylmethanol, that the alkyl–oxygen bond is broken in certain experimental conditions.[2] However our tracer experiments did not detect any alkyl–oxygen bond fission in diphenylmethyl formate or acetate; but a small component in the acetate might have been obscured by oxygen exchange between diphenylmethanol and the water of the solvent.

As a possible explanation of the acyl–oxygen bond fission in diphenylmethyl formate and acetate it was suggested that there might be intramolecular hydrogen bonding between the carbonyl-oxygen atom and a hydrogen atom on the alkyl-carbon atom. It was hoped that examination of the hydrolysis of 9-fluorenyl acetate, and of the kinetic effect of deuterium substitution in the " alkyl " group, might provide useful information.

Results.—Bond fission. The position of bond fission was determined by isolating the alcohol product with the water of the solvent enriched in ^{18}O (Table 1). The acyl–oxygen bond is broken in the alkaline hydrolysis of 9-fluorenyl acetate, and the same bond fission is assumed

TABLE 1. *Bond fission in the hydrolysis of 9-fluorenyl acetate.*

Solvent: dioxan–water 70 : 30 v/v. Temp. 100°, except for the alkaline hydrolysis which was at 25°. Isotopic abundance of water 0·790 atom % excess. Abundance of alcohol in terms of atom % excess.

	Hydrolyses			Control	
Reagent	0·4M-NaOH	0·5M-H_2SO_4	(Neutral)	0·05M-H_2SO_4	0·2M-AcOH
Time (hr.)	10	15	1600	15	1600
Abundance of alcohol	0·030	0·140	0·056	0·250	0·014

[9-Fluorenyl acetate]: *ca.* M/3 in hydrolysis. [Fluoren-9-ol]: *ca.* M/3 in control experiments.

for the alkaline hydrolysis of diphenylmethyl acetate, by analogy with results for 4-methoxydiphenylmethyl acetate [3] and diphenylmethyl formate.[1] A similar result is found, within the limits imposed by oxygen exchange between the alcohol and water, for the acid hydrolyses of

* Part VI, *J.*, 1958, 3248.

[1] Bunton, Day, Flowers, Sheel, and Wood, *J.*, 1957, 963.
[2] Harvey and Stimson, *J.*, 1956, 3629.
[3] Bunton and Hadwick, *J.*, 1957, 3013.

9-fluorenyl and diphenylmethyl acetate.[1] The fluoren-9-ol from hydrolysis in initially neutral solution is slightly enriched in ^{18}O; this may correspond to a minor contribution by mechanism $B_{Al}1$.

Kinetic form for hydrolysis. The hydrolysis is accelerated by hydrogen and hydroxide ions. In initially neutral solution there is a slow hydrolysis which is not autocatalysed, and therefore is a reaction of the ester molecule with water. The acid hydrolysis follows the law, Rate = $k_A[H^+][Ester]$, with $10^3k_A = 2{\cdot}58$ (sec.$^{-1}$ mole^{-1} l.) at 100·1°. The Arrhenius equations are: acid, $k_A = 1{\cdot}1 \times 10^7 \exp(-16{,}400/\boldsymbol{R}T_A)$; alkaline, $k_2 = 2{\cdot}4 \times 10^8 \exp(-13{,}400/\boldsymbol{R}T_A)$; neutral, $k_1 = 4{\cdot}2 \times 10^{11} \exp(-29{,}900/\boldsymbol{R}T_A)$. The rates are similar to those for diphenylmethyl acetate, and are unaffected by deuterium substitution on the alkyl-carbon atom.

TABLE 2. *Rates of hydrolysis in aqueous dioxan.*

Solvent: dioxan–water 70 : 30 v/v. Protio-compound unless otherwise specified.

(A) 9-*Fluorenyl acetate.*

(i) Alkaline hydrolysis at 25° (except where otherwise specified).

	Protio			Deutero	
10^2k_2 (sec.$^{-1}$ mole^{-1} l.)	3·57 [a]	3·60 [b]	0·45 *	3·75 [c]	3·69 [b]

* Temp. 0°. [a, c] Conductimetric, mean of 5 and 2 values respectively. [b] Titration, mean of 2 values.

(ii) Acid hydrolysis at 100·1° (except where otherwise specified).

$[H_2SO_4]$ (M) ...	0·0239	0·0396	0·0406	0·0496		0·0506	0·0570	0·0706	0·074
10^4k_1 (sec.$^{-1}$)	0·54	0·94	1·06	1·23	1·20 †	1·28	1·48	1·73	0·0398 *

* Temp. 44·6°. † Deutero compound.

(iii) Neutral hydrolysis.

At 100·1° $10^6k_1 = 1{\cdot}35$ (sec.$^{-1}$); at 82·0° $10^7k_1 = 1{\cdot}73$ (sec.$^{-1}$).

(B) *Diphenylmethyl acetate.*

Alkaline hydrolysis at 25°.

	Protio		Deutero
10^2k_2 (sec.$^{-1}$ mole^{-1} l.)	1·20 *	1·21	1·19

* Conductimetric, mean of two values; other values were obtained by titration.

Discussion.—The position of bond fission and the kinetic form show that the mechanism of the alkaline hydrolysis of diphenylmethyl and 9-fluorenyl acetate is $B_{Ac}2$. Similarly, in acid solution the acyl–oxygen bond is broken in the hydrolysis of 9-fluorenyl acetate. The Arrhenius parameters are in the range considered to be typical of acid-catalysed bimolecular hydrolyses.[2,4]

The value of k_2 for the basic hydrolysis of 9-fluorenyl acetate is *ca.* three times that for diphenylmethyl acetate, which is itself very similar to that for the 4-methoxydiphenylmethyl acetate.[3] The rate of nucleophilic attack on the acyl-carbon atom of a carboxylic ester is little affected by the electronic properties of the alkyl group; it is much more sensitive to the nature of the group attached to the reaction centre. Probably the slightly greater reactivity of 9-fluorenyl acetate is caused by the greater electron-attraction of the fluorenyl than of the diphenylmethyl group. Diphenylmethyl formate is much more reactive towards hydroxide ions than is the acetate;[1] similar rate differences are observed for the aliphatic series.

The rates of acid hydrolysis of 9-fluorenyl and diphenylmethyl acetate are very similar, but the diphenylmethyl ester is the more reactive. The factor is *ca.* three (Table 2), although the conditions of hydrolysis of the two esters are slightly different. It is not easy to interpret such small rate differences for reactions with specific hydrogen-ion catalysis, because the rate equation is made up of an equilibrium constant for the formation of the conjugate acid and a rate constant for its breakdown to products. The effects of structural changes on these constants cannot, in general, be evaluated independently, and electronic displacements may affect these constants in opposite directions. However the mechanism

[4] Long and Pritchard, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.

$A_{Ac}2$, like $B_{Ac}2$, is not usually much affected by the electronic properties of the alkyl group.[5] Again the formate is more reactive than the acetate.[1]

It was suggested earlier [1] that the reactivity of the acyl-carbon atom of a carboxylic ester might be increased by hydrogen bonding between the carbonyl-oxygen atom and a hydrogen atom attached to the alkyl-carbon atom. The similarity of the rates of hydrolysis of 9-fluorenyl and diphenylmethyl acetate, in both acid and alkaline solution, suggests that there is no catalysis by such an intramolecular hydrogen bonding. This conclusion is strengthened by the negligible effect which the replacement of protium by deuterium has on the rates of both acid- and base-hydrolysis, because the extent of an intramolecular hydrogen-bonding, and therefore the rates of hydrolysis, should be affected by such a substitution. It is conceivable, but unlikely, that the change in stability which replacement of protium by deuterium brings about in the initial state, is very close to that which it brings about in the transition state, but it is much simpler to believe that interactions between the carbonyl-oxygen atom and hydrogen atoms of the alkyl group are not kinetically significant in ester hydrolyses. (Any inductive, or other, effect of deuterium relayed through the carbon and oxygen atoms would have a negligible kinetic effect at the acyl-carbon atom.[6])

Experimental.—Materials. Deuterated diphenylmethanol and fluoren-9-ol were prepared by reduction of corresponding ketones with lithium aluminium deuteride in dry ether. The aluminium complex was destroyed by the cautious addition of isotopically normal water. Diphenylmethyl [^{2}H]alcohol, recrystallised from light petroleum, had m. p. 66—67° (yield 80%). Fluoren-9-[^{2}H]ol, recrystallised from aqueous ethanol, had m. p. 152—153° (yield 95%).

Fluoren-9-ol, prepared by reduction of the ketone with lithium aluminium hydride, had m. p. 155°.

The acetates, prepared by use of acetic anhydride, were decolorised with charcoal and recrystallised from light petroleum. Diphenylmethyl acetate had m. p. 42°; its deutero-analogue had m. p. 41—42°; 9-fluorenyl acetate had m. p. 70°; its deutero-analogue had m. p. 69—70°.

Solvents were made up by weight from purified dioxan and water to correspond to dioxan–water 70 : 30 v/v.

Position of bond fission. Tracer experiments were made with the solvent water enriched in ^{18}O. The alcohol, isolated from hydrolysis under kinetically controlled conditions, was purified by recrystallisation from light petroleum, and dried in a vacuum-desiccator. The isotopic abundance of samples was determined by pyrolysing them *in vacuo* on a carbon tube heated by an R.F. induction furnace. The carbon monoxide so produced was analysed mass-spectrometrically.

Kinetic runs. The hydrolyses were followed by acid–base titration for acid, alkaline, and initially neutral solutions. Some runs in alkaline solution were followed conductimetrically.[7] Stoppered flasks or cells were used for experiments at ≤25°; sealed tubes were used at the higher temperatures.

Two runs on protio- and deutero-diphenylmethyl acetate are detailed.

Temp. 25°. Followed by acid base titration.
Initial [OH^-] = $4{\cdot}00 \times 10^{-2}$M; [protio-ester] = $2{\cdot}38 \times 10^{-2}$M; [deutero-ester] = $2{\cdot}35 \times 10^{-2}$M.

Time (min.)	0	4	9	16	22	31·5	32	44	58	78
[OH^-]	18·32	16·80	15·29	14·11	13·36	—	12·11	11·18	10·43	9·64
[Protio-ester]	10·90	9·38	7·87	6·69	5·94	—	4·69	3·76	3·01	2·22
[OH^-]	18·32	16·53	15·31	14·08	13·26	12·31	—	11·20	10·40	9·62
[Deutero-ester]	10·79	9·00	7·78	6·55	5·73	4·78	—	3·67	2·87	2·09

(Concn. expressed as c.c. of 0·0218N-HCl per 10 c.c. portion of reaction mixture.)

10^2k_2 (sec.$^{-1}$ mole^{-1} l.): protio 1·21; deutero 1·19 (calcd. graphically from the integrated second-order rate equation).

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[5] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.
[6] Halevi, *Tetrahedron*, 1957, **1**, 174.
[7] Daniels, Mathews, Williams, Bender, and Alberty, "Experimental Physical Chemistry," McGraw-Hill, New York, 1956, p. 131.

747. N-*Oxides and Related Compounds. Part XV.*[1] *Ultraviolet Spectra of 2'-(Carbamoyl- and Ethoxycarbonyl-)vinylpyridines and their* 1-*Oxides.*

By A. R. Katritzky, A. M. Monro, and J. A. T. Beard.

Dipole moments of 4-substituted derivatives show that the pyridine 1-oxide ring can create both a deficit and a surfeit of electrons at the 4-position more readily than the pyridine ring.[2] Carbonyl-stretching frequencies in acyl derivatives show in addition that the pyridine 1-oxide ring can make electrons available more readily in the 4- than in the 3-position, but that the reverse is true of the pyridine ring.[3] To study the effect of these differences on ultraviolet spectra, we examined the isomeric β-pyridylacrylic esters and amides and their 1-oxides (Table); the acids were not used because of complications from zwitterion formation.

Ultraviolet spectra (λ *in* mμ).

	Neutral molecule [a]						Conjugate acid [b]			
Subst.	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$
(A) *Ethyl β-substituted acrylates.*										
Ph	204	11·9	217 222 *	13·1 11·2	279	21·6	(Not applicable)			
4-Pyridyl ...	204	13·3	—	—	259	21·9	—	—	271	23·4
3-Pyridyl ...	206	12·5	262	17·1	282 *	13·5	218 *	13·0	255 280 *	18·0 9·9
2-Pyridyl ...	206	14·5	249	12·7	290	15·0	206 241	14·4 8·4	290	18·6
(B) *Ethyl β-substituted acrylate* N-*oxides.*										
4-Pyridyl ...	221	12·4	—	—	300	18·9	203	15·1	278	23·2
3-Pyridyl ...	206	10·4	—	—	252	28·6	223	17·4	261	15·4
2-Pyridyl ...	—	—	244	26·7	286	13·2	216 251	14·2 8·4	294	15·4
(C) *β-Substituted acrylamides.*										
Ph	204	16·4	216 222 *	18·6 16·4	275	23·9	(Not applicable)			
4-Pyridyl ...	205	14·4	—	—	259	21·7	—	—	271	23·2
3-Pyridyl ...	206	13·4	259	19·0	284 *	13·4	224	14·7	255	23·4
2-Pyridyl ...	206	16·0	249	14·6	289	15·2	206 241	14·2 9·9	291	18·0
(D) *β-Substituted acrylamide* N-*oxides.*										
4-Pyridyl ...	221	13·5	—	—	300	20·7	207	13·8	282	24·6
3-Pyridyl ...	—	—	—	—	251	28·9	222	14·1	265	16·4
2-Pyridyl ...	—	—	239	28·7	281	13·6	221 256 *	14·0 9·3	296	16·6

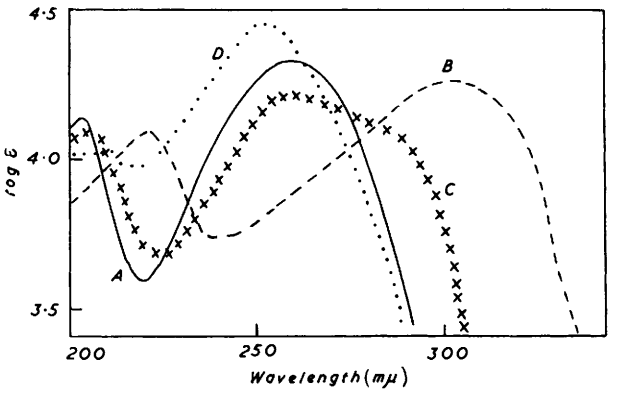
* Inflection. [a] In aqueous phosphate buffer of pH 9·7, except that the first entry is for aqueous ethanol (70 : 30 v/v), and the eighth for water. [b] Entries nos. 2—4 and 9—11 in aqueous N-sulphuric acid, others in 20N-sulphuric acid.

In these compounds, the band of longest wavelength probably corresponds to a π–π* transition, the promotion of an electron between molecular orbitals including both the ring and the side chain. The greater the conjugation between ring and side chain, the lower will be the energy of the first excited state, and thus the longer the wavelength of the bands. The side chains act as electron-acceptors more readily than electron-donors; in agreement, the wavelength is longer, and the conjugation thus stronger, in the 4- than in the 3-pyridine 1-oxide, but in the 3- than in the 4-pyridine (see Figure). In the conjugate acids, the electron-donor ability of the rings is much impaired; the conjugation is probably

[1] Part XIV, Katritzky and Hands, *J.*, 1958, 2195.
[2] Katritzky, Randall, and Sutton, *J.*, 1957, 1769; Bax, Katritzky, and Sutton, *J.*, 1958, 1254.
[3] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.

mainly by donation of electrons from the side chain to the ring. In agreement the wavelength is longer in the order 2 > 4 > 3 for both the pyridines and the 1-oxides, and in each one of these positions the 1-oxide absorbs at longer wavelengths than the corresponding pyridine. Donation to the ring may be important in both the 2-substituted compounds, even in the neutral molecules. These results parallel those for the infrared C:C stretching band.[3]

Ultraviolet spectra of (*A*) *ethyl* 4-*pyridylacrylate*, (*B*) *its* 1-*oxide*, *and* (*C*) *ethyl* 3-*pyridylacrylate and* (*D*) *its* 1-*oxide*.



Experimental.—Preparation of the 3- and the 4-pyridyl compounds has been described.[4,5] Ethyl cinnamate was a redistilled commercial sample; the amide was prepared by a standard method.

β-2-*Pyridylacrylamide*. Ethyl β-2-pyridylacrylate (62%), b. p. 159°/22 mm. (lit.,[6] b. p 161/25 mm.), was prepared as for the 4-analogue; [4] with aqueous-ethanolic ammonia it gave the *amide* (96%), rhombs (from ethanol), m. p. 141° (Found: C, 64·5; H, 5·4. $C_8H_8ON_2$ requires C, 64·8; H, 5·4%).

Oxidation [5] of the above ester gave the *ethyl ester* 1-*oxide* (56%), rhombs (from ethyl acetate or benzene), m. p. 68—68·5° (Found: C, 61·9; H, 5·9; N, 7·1. $C_{10}H_{11}ON_3$ requires C, 62·2; H, 5·7; N, 7·3%), which afforded (as above) the *amide* 1-*oxide* (67%), prisms (from ethanol), m. p. 208—209° (darkens above 200°) (Found: C, 58·3; H, 5·0; N, 17·0. $C_8H_8O_2N_2$ requires C, 58·5; H, 4·9; N, 17·1%).

Oxidation [5] gave the *acid* 1-*oxide* (52%), which separated from pentyl alcohol in needles, m. p. 240° (decomp.; darkens above 225°) (Found: C, 58·4; H, 4·1; N, 8·4. $C_8H_7O_3N$ requires C, 58·2; H, 4·3; N, 8·45%).

This investigation was largely carried out during the tenure (by A. R. K.) of an I.C.I. Fellowship. The spectra were measured by Miss V. Brown, under the supervision of Dr. F. B. Strauss, on a Cary recording spectrophotometer.

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THE CHEMICAL LABORATORY, CAMBRIDGE UNIVERSITY. [*Received, March 17th*, 1958.]

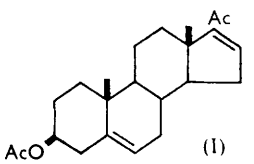
[4] Katritzky, *J.*, 1955, 2581.
[5] Katritzky and Monro, *J.*, 1958, 150.
[6] Löffler and Flügel, *Ber.*, 1909, **42**, 3423.

748. *The Michael Reaction of 3β-Acetoxypregna-5 : 16-dien-20-one and Malonic Ester.*

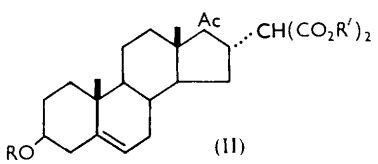
By Peter Bladon.

The ability of a wide variety of nucleophilic reagents to add to the double bond of Δ^{16}-unsaturated 20-oxo-steroids is well known. Thus, reactions with alkoxides,[1] amines,[2] and thiols[3] lead to the formation of 16α-alkoxy-, 16α-alkylamino-, and 16α-alkylthio-derivatives, respectively. Nitroparaffins under appropriate conditions[4] give 16α-nitroalkyl derivatives. The possibility that derivatives of progesterone containing carboxyl or methoxycarbonyl functions might have useful biological properties prompted extension of this type of reaction.

Michael reaction between 3β-acetoxypregna-5 : 16-dien-20-one (I) and sodiomalonic ester gave, after brief hydrolysis with aqueous alkali and acid treatment, the expected 3β-hydroxy-20-oxopregn-5-en-16α-ylmalonic acid (IIa). If the hydrolysis step was omitted, the product was the ethyl ester (IIb) which was, however, not obtained crystalline. Prolonged hydrolysis resulted in poor yields of the acid, due to (*a*) the splitting of the product into hydrolysed starting materials and (*b*) further changes to an amorphous product from which a small amount of crystalline material was obtained. The tentative formulation of this as (III) is supported by the fact that the ultraviolet spectra in neutral and alkaline solution resemble the corresponding spectra of 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (dimedone). Further, the infrared spectrum had a strong band at 1590 cm.$^{-1}$, characteristic of the enol form of a β-diketone. The ill-defined melting point and poor recovery on crystallisation are probably due to the presence of (C-17) isomeric substances, and two enol forms.



(I)



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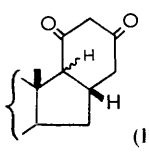
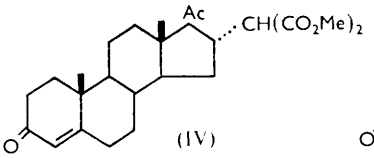
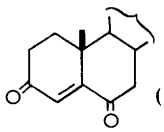


(III)

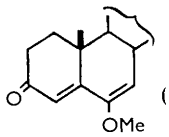
(IIa; R = R′ = H)
(IIb; R = Ac or H, R′ = Et)
(IIc; R = H, R′ = Me)
(IIId; R = Ac, R′ = Me)
(IIe; R = B_2, R′ = Me)



(IV)



(V)



(VI)

Oxidation of the methyl ester (IIc) by chromic acid–sulphuric acid in acetone,[5] gave either of two products depending on the amount of oxidant used. The first, obtained with 1 mole of oxidant, was a mixture of the Δ^5-3-ketone and starting material. This

[1] Gould, Gruen, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 2510; Hirschmann, Hirschmann, and Daus, *ibid.*, 1952, **74**, 539.
[2] Gould, Shapiro, and Hershberg, *ibid.*, 1954, **76**, 5567.
[3] Rosenkranz, Djerassi, and Romo, U.S.P. 2,697,108 (*Chem. Abs.*, 1955, **49**, 14044).
[4] Dodson, U.S.P. 2,697,109 (*Chem. Abs.*, 1955, **49**, 14042).
[5] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.

was treated with mineral acid, to yield, after purification, the desired dimethyl 3 : 20-dioxopregn-4-en-16α-ylmalonate (IV). Excess of oxidant gave dimethyl 3 : 6 : 20-trioxopregn-4-en-16α-ylmalonate (V), which on treatment with acidic methanol gave dimethyl 6-methoxy-3 : 20-dioxopregna-4 : 6-dien-16α-ylmalonate (VI), whose ultraviolet absorption spectrum shows peaks at 205, 249, and 304 mμ. Windaus, Inhoffen, and Reichel [6] record a spectrum with peaks at 247 and 295 mμ (in ether) for 6-ethoxycholesta-4 : 6-dien-3-one, formed analogously from cholest-4-ene-3 : 6-dione and acidic ethanol.*

Experimental.—M. p.s were determined on a Kofler hot stage. Unless otherwise stated rotations were determined in chloroform at room temperature, ultraviolet spectra in ethanol, and infrared spectra as Nujol mulls.

3β-*Hydroxy*-20-*oxopregn*-5-*en*-16α-*ylmalonic Acid* (IIa). Sodium (200 mg., 8 mmoles) was dissolved in ethanol (25 ml.) and diethyl malonate (1·6 g., 10 mmoles) was added followed by 3β-acetoxypregna-5 : 16-dien-20-one (712 mg.; 2 mmoles). The mixture was refluxed for 3 hr. with exclusion of moisture; then a solution of potassium hydroxide (4 g.) in 50% v/v aqueous ethanol (20 ml.) was added and refluxing continued for 5 min. Addition of water and extraction with ether afforded a small neutral fraction (4 mg.). Acidification of the aqueous layer gave a white solid (782 mg.). Recrystallisation of the dried material from methanol–acetone gave 3β-*hydroxy*-20-*oxopregn*-5-*en*-16α-*ylmalonic acid* (IIa) as needles, m. p. 250—253°, $[\alpha]_D$ +36° (*c*, 0·40 in methanol) (Found: C, 68·55; H, 8·25. $C_{24}H_{34}O_6$ requires C, 68·9; H, 8·2%); $\nu_{max.}$ 1740 m, 1700 m, and diffuse peaks at 3460 and 3220 cm.$^{-1}$.

If the reaction mixture was extracted with ether after the initial refluxing, there was isolated the corresponding diethyl ester (IIb) as an oil (866 mg.), and an acidic fraction (243 mg., soluble in aqueous potassium hydrogen carbonate). Brief hydrolysis of the neutral ester gave the acid in good yield. Hydrolysis of the acidic fraction gave an amorphous acidic material which was probably identical with material described below.

In another experiment (on half the scale) hydrolysis for 2 hr. under reflux gave a neutral fraction (219 mg.) from which 3β-hydroxypregna-5 : 16-dien-20-one could be isolated together with the acid described above (118 mg.).

In a third experiment, hydrolysis at room temperature overnight afforded a negligible amount of neutral fraction together with gelatinous acidic material (750 mg.). Recrystallisations from methanol and dimethylformamide–methanol gave rhombs of 3β-*hydroxy*-16α : 24-cyclo-21-*norchol*-5-*en*-20 : 23-*dione* (III), m. p. 235—245° (decomp.) (change of form into needles at 200—220°), $[\alpha]_D$ +55·4° (*c* 0·5 in pyridine) (Found: C, 74·3; H, 8·95. $C_{23}H_{32}O_3,CH_3OH$ requires C, 74·2; H, 9·3%); $\lambda_{max.}$ 254·5 mμ, ε 14,000; $\lambda_{max.}$ (at pH 9·5) 285 mμ, ε 22,000; $\nu_{max.}$ 1700 w, 1640 w, 1590 s and a broad hydroxyl peak in the 3000 cm.$^{-1}$ region. Dimedone under similar conditions had $\lambda_{max.}$ 257 mμ, ε 16,600 and $\lambda_{max.}$ (at pH 9·5) 282 mμ, ε 25,700.

Dimethyl 3β-*hydroxy*-20-*oxopregn*-5-*en*-16α-*ylmalonate* (IIc). The foregoing acid (2·08 g.; m. p. 200—250°) suspended in a little methanol was treated with excess of diazomethane in ether for 20 min. After destruction of diazomethane the solution was evaporated to dryness. Crystallisation from methanol–ether and chromatography of the material in the mother liquors gave material, m. p. 200° (969 mg.). The pure *dimethyl ester* (IIc) formed needles, m. p. 200—202°, $[\alpha]_D$ +22° (*c* 0·38), from acetone (Found: C, 69·95; H, 8·75. $C_{26}H_{38}O_6$ requires C, 69·95; H, 8·6%); $\nu_{max.}$ 3560 w, 3500 w, 1740 s, 1720 s, 1698 s cm.$^{-1}$.

Acetylation of this ester with acetic anhydride and pyridine at room temperature gave *dimethyl* 3β-*acetoxy*-20-*oxopregn*-5-*en*-16-*ylmalonate* (IId), crystals from aqueous methanol, m. p. 124—125° (solidifying and remelting at 138—139°), $[\alpha]_D$ +8·8° (*c* 0·69) (Found: C, 69·0; H, 8·6. $C_{28}H_{40}O_7$ requires C, 68·8; H, 8·25%); $\nu_{max.}$ 1741, 1710, 1225 cm.$^{-1}$. The *benzoate* (IIe) prepared with benzoyl chloride and pyridine formed needles, m. p. 200—201°, $[\alpha]_D$ +32·6° (*c* 0·59), from acetone–methanol (Found: C, 71·75; H, 7·8. $C_{33}H_{42}O_7$ requires C, 72·0; H, 7·7%); $\nu_{max.}$ 1741, 1700, 707 cm.$^{-1}$.

Dimethyl 3 : 20-*dioxopregn*-4-*en*-16α-*ylmalonate* (IV). Dimethyl 3β-hydroxypregn-5-en-16α-ylmalonate (223 mg.) in acetone (15 ml.) was stirred vigorously at room temperature and chromic acid solution added (0·15 ml. of a solution of 66·7 g. of chromium trioxide and 53 ml. of concentrated sulphuric acid made up to 250 ml. with water). After 1 min., methanol was

* The author is very grateful to a Referee for pointing out the analogy with Windaus's compound.

[6] Windaus, Inhoffen, and Reichel, *Annalen*, 1934, **510**, 248.

added followed by water in excess. The product was isolated by extraction with ether, the extracts being washed with aqueous potassium hydrogen carbonate, and dried (Na_2SO_4). The residue (215 mg.) in methanol (15 ml.) was warmed with 10% aqueous sulphuric (2 ml.) for 10 min. Addition of water and extraction with ether (as before) afforded a solid residue. Chromatography on alumina (5 g.) gave *dimethyl* 3 : 20-*dioxopregn*-4-*en*-16α-*ylmalonate* (IV) (105 mg.), eluted with benzene, and forming prisms (from dichloromethane–*iso*propyl ether), m. p. 142—145°, $[\alpha]_D$ +117·5° (*c* 0·62) (Found: C, 70·45; H, 8·4. $C_{26}H_{36}O_6$ requires C, 70·25; H, 8·15%); $\lambda_{max.}$ 240 mμ, ε 15,700; $\nu_{max.}$ 1764, 1745, 1706, 1681, 1621 cm.$^{-1}$. Elution of the column with ether gave starting material, m. p. 200—202° (42 mg.).

Dimethyl 3 : 6 : 20-*trioxopregn*-4-*en*-16α-*ylmalonate* (V). To vigorously stirred dimethyl 3β-hydroxypregn-5-en-16α-ylmalonate (203 mg.) in acetone (10 ml.) the foregoing chromic acid solution (1 ml.) was added at 20°. The excess of oxidant was destroyed after 5 min. by adding dilute hydrochloric acid and sodium sulphite. Ether extraction gave a solid (144 mg.) which on crystallisation from methanol gave *dimethyl* 3 : 6 : 20-*trioxopregn*-4-*en*-16α-*ylmalonate* as pale yellow prisms, m. p. 171—172°, $[\alpha]_D$ +11·9° (*c* 0·72) [Found: C, 67·8; H, 7·8%; *M* (Rast), 478. $C_{26}H_{34}O_7$ requires C, 68·1; H, 7·5%; *M*, 459]; $\lambda_{max.}$ 252 mμ, ε 11,600; $\nu_{max.}$ 1759—1737, 1691, and 1607 cm.$^{-1}$.

Dimethyl 6-*methoxy*-3 : 20-*dioxopregna*-4 : 6-*dien*-16α-*ylmalonate* (VI). The foregoing triketone (75 mg.), in methanol (5 ml.), was treated with perchloric acid (2 drops of 70% aqueous solution) and warmed. After 5 min. water was added, and the product isolated by extraction with ether. Recrystallisation from methanol gave the *enol methyl ether* (VI), m. p. 199—200°, $[\alpha]_D$ +62·7° (*c* 0·75) (Found: C, 69·05, 69·05; H, 8·15, 8·2; OMe, 21·5. $C_{27}H_{36}O_7$ requires C, 68·6; H, 7·7; OMe, 19·7%); $\lambda_{max.}$ 205, 249, and 304 mμ, ε 5,100, 8,540, and 16,100; $\nu_{max.}$ 1742, 1705, 1675, 1621, 1585 cm.$^{-1}$.

The author thanks Dr. F. Sondheimer for a gift of dehydropregnenolone acetate. He is also indebted to Mr. W. McCorkindale for the microanalyses, to Miss N. Caramando for the infrared spectra, and to Mrs. D. Thomson and Miss I. O'Hagan for the ultraviolet spectra.

The Royal College of Science and Technology,
Glasgow, C.1. [*Received, March 27th*, 1958.]

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749. *The Cleavage of Diaryl Ethers by Grignard Reagents in the Presence of Cobaltous Chloride. Part III.*[1] *Fluorine-containing Diphenyl Ethers.*

By R. L. Huang.

The cleavage of substituted diphenyl ethers by Grignard reagents in the presence of cobaltous chloride, assumed to proceed *via* aryloxy-radicals, enabled a comparison to be made of the relative stabilising influences of substituent groups on such radicals.[1] Conclusions thus reached in general support Ingold's early postulate [2] that electropositivity in substituents stabilises such radicals with respect to hydrogen, but also suggest that

Table 1. *Cleavage of* $R{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_4R'$.

R	R′	Ether cleaved (%)	F (%) in phenolic mixture		Mean F (%)	$R{\cdot}C_6H_4{\cdot}OH$ (moles %)
p-F	H	42	9·8	9·8	9·8	54
p-F	*m*-Me	26	3·3	3·2	3·3	20
m-CF_3	H	83	29·0	28·7	28·9	73
m-CF_3	*m*-Me	17	17·0	17·5	17·3	39
m-CF_3	*p*-OMe	14	21·7	22·0	21·9	56

resonance is a more decisive contributing factor toward radical stability. The cleavage of five diphenyl ethers containing the *p*-fluoro- and the *m*-trifluoromethyl substituents is now reported.

Results of fission experiments are summarised in Table 1. If the intermediate formation of aryloxy-radicals is assumed, the cleavage of *p*-fluorophenyl phenyl ether to

[1] Huang, *J.*, 1954, (*a*) (Part I), p. 3084, (*b*) (Part II), p. 3088.
[2] Ingold, *Trans. Faraday Soc.*, 1934, **30**, 52.

a phenolic mixture containing more than 50 moles % of *p*-fluorophenol indicates that reaction in the main proceeds by way of the *p*-fluorophenoxy-, rather than the phenoxy-, radical, and hence that the former radical is the more stable. Thus in stabilising effect on aryloxy-radicals, *p*-F > H. Similarly, from the direction of cleavage of the other ethers, it would be concluded that: *m*-Me > *p*-F; *m*-CF_3 > H; *m*-Me > *m*-CF_3; and *m*-CF_3 > *p*-OMe. Combining these, we have: *m*-Me > *p*-F > H; and *m*-Me > *m*-CF_3 > *p*-OMe.

In view of the relatively small quantities of ethers used in the cleavage experiments, and of the low percentage reaction in some cases, it is considered that the data obtained give only an indication of the order of stabilising effects.

TABLE 2. *Synthesis of* R·C_6H_4·O·C_6H_4·R′.

R	R′	Phenol, starting material	Yield (%)	B. p./ m.m.	n_D (temp.)	Found (%) C	Found (%) H	Formula	Required C	Required H
p-F	H	Phenol	66	96—98°/2	1·5557 (23°)	76·9	4·85	$C_{12}H_9OF$	76·6	4·8
p-F	*m*-Me	*m*-Cresol	75	81°/0·5	1·5500 (24°)	77·7	5·6	$C_{13}H_{11}OF$	77·2	5·45
m-CF_3	H	Phenol	66	88—89°/2	1·5111 (24°)	65·7	4·1	$C_{13}H_9OF_3$	65·5	3·8
m-CF_3	*m*-Me	*m*-Cresol	30	96—98°/0·5	1·5119 (22°)	66·8	4·5	$C_{14}H_{11}OF_3$	66·7	4·4
m-CF_3	*p*-OMe	*p*-MeO·C_6H_4·OH *	19	90—92°/0·1	1·5188 (23°)	62·6	4·2	$C_{14}H_{11}O_2F_3$	62·7	4·1

* 5 moles used per mole of halide, with 2·5 mols. of potassium hydroxide, the mixture being heated at 180° for 4 hr., 210° for 4 hr., then 230° for another 4 hr.

Experimental.—Synthesis of ethers. The following modification of the Ullmann synthesis was adopted. The phenol (10 mols. per mol. of the halide used), potassium hydroxide (5 mols.) and copper powder were heated in a Pyrex glass tube at 180° under a stream of nitrogen until most of the steam formed had been removed. After addition of the halide the tube was sealed and heated at 180° for 2 hr., then at 240° for 3 hr. The reaction mixture was treated with 10% aqueous sodium hydroxide, and the product isolated by extraction with diethyl ether. The new ethers prepared are listed in Table 2.

p-Bromofluorobenzene was obtained from Light & Co., and *m*-chlorobenzotrifluoride was prepared, in three steps, from benzotrifluoride.[3]

Cleavage experiments. The same procedure as described in Part I was followed, except that a 10 mol. excess of the Grignard reagent and a 5 mol. excess of anhydrous cobaltous chloride were employed. Cleavage was carried out on 2·0—2·5 g. of the ether, except for phenyl *m*-trifluoromethylphenyl ether and *p*-methoxyphenyl *m*-trifluoromethylphenyl ether, of which 4·2 g. and 3·4 g., respectively, were used.

Microanalyses are by Dr. W. Zimmermann, Melbourne.

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, April 14th*, 1958.]

[3] Whalley, *J.*, 1949, 3016.

750. *Direct Oxidation of Indoles to Oxindoles.*

By C. E. DALGLIESH and W. KELLY.

PERSULPHATE converts indoles and aromatic amines into *O*-sulphates of phenolic derivatives, *e.g.*, indole gives indoxyl *O*-sulphate (indican) and anthranilic acid gives the *O*-sulphates of 3- and 5-hydroxyanthranilic acid.[1] We have found that under the usual, strongly alkaline, conditions skatole is converted into a large number of products, whose properties suggest that in almost all cases the pyrrole ring has opened. Under mildly acid conditions (pH 4—5) a much higher proportion of the products retains the indole nucleus. The major product is 3-methyloxindole.

Skatole is directly oxidised to 3-methyloxindole by peracetic acid,[2] but the yield is low (*ca.* 14%) and the isolation lengthy. Other methods for converting indoles into oxindoles

[1] Boyland, Sims, and Williams, *Biochem. J.*, 1956, **62**, 546.
[2] Witkop, *Annalen*, 1947, **558**, 98.

are: (i) reaction [3] with sulphur monochloride to give the 2 : 2′-disulphide which is then reductively hydrolysed, and (ii) treatment with ferric chloride in the presence of diethylamine to give as one of many products an ether (*e.g.*, 3-methylindol-2-yl 2 : 3-dihydro-3-methylindol-2-yl ether from skatole) which can be split to the substituted indole and substituted oxindole. Overall yields are low in both methods.

In the present simple method the conversion of skatole into 3-methyloxindole was appreciably higher (about 38%). Our interest was in products other than 3-methyloxindole and we have not attempted to find optimal conditions for oxindole formation. The reaction also occurs with 3 : 5-dimethylindole. Indole itself does not give oxindole, but oxidises at the 3-position to give indican (cf. ref. 1).

A possible mechanism of reaction would be formation of the 2-hydroxyindole *O*-sulphate, followed by hydrolysis to the enol form of the oxindole. However, the oxindole is formed, though in lower yield, even at alkaline pH under conditions in which phenolic sulphate esters are usually stable.

Experimental.—The oxidation of skatole to 3-methyloxindole. A solution of potassium persulphate (11·5 g.) and sodium acetate (6 g.) in water (400 ml.) was added to one of skatole (5 g.) in ethanol (250 ml.). The mixture was kept for 2 hr. at room temperature, and then extracted with ether (4 × 300 ml.). The organic solvents were removed, and the residue was again extracted with ether. This second extract was dried and concentrated, and the residue distilled under vacuum (water pump). Unchanged skatole (1·3 g.) was followed by a main fraction, distilling at 175—180° as a yellow syrup which slowly solidified. The product (1·6 g.) was recrystallised from benzene–light petroleum, and then from water. M. p. and mixed m. p. with an authentic sample of 3-methyloxindole were 121—122° (Found: C, 73·4; H, 6·2; N, 9·4. Calc. for C_9H_9ON: C, 73·4; H, 6·2; N, 9·5%). The yield was 28%, or allowing for recovered skatole, 38%.

Oxidation of 3 : 5-dimethylindole. A solution of potassium persulphate (1·10 g.) and sodium acetate (0·6 g.) in water (40 ml.) was added to one of 3 : 5-dimethylindole (0·5 g.) in ethanol (25 ml.) and the mixture kept for 2 hr. at room temperature. Extraction was as for skatole. The residue was fractionally sublimed. Unchanged indole sublimed at 100—110° (water pump) and a yellow gum at 130—140°. The gum was recrystallised from benzene–light petroleum (prisms), then from water (needles), and was then sublimed to give 3 : 5-*dimethyloxindole*, m. p. 154—155° (Found: C, 74·9; H, 7·5. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·9%).

We thank the Medical Research Council for support.

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Ducane Road, London, W.12. [*Received, April 22nd*, 1958.]

[3] Wieland, Weiberg, Fischer, and Horlein, *Annalen*, 1954, **587**, 146; Wieland, Weiberg, and Dilger, *ibid.*, 1955, **592**, 69; Freter, Axelrod, and Witkop, *J. Amer. Chem. Soc.*, 1957, **79**, 3191.

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751. *The Chlorination and Bromination of Hydrocarbons under Influence of High-energy Radiation and Other Initiating Agents.*

By R. A. Cox and A. J. Swallow.

It is known that high-energy radiation in common with actinic radiation and free radicals will catalyse the halogenation of organic compounds.[1,2] High-energy radiation interacts with matter to produce in the first instance ions, excited molecules, free radicals, and molecular products from all constituents of a mixture, and it might be expected that the free radicals would initiate the same chain reaction as is produced by other free-radical initiators. On the other hand, because of the unusual nature of the primary act, the

[1] Alyea, *J. Amer. Chem. Soc.*, 1930, **52**, 2743.
[2] Harmer, Martin, and Anderson, *Chem. Eng. Progr. Symp.*, 1954, **50**, 253; *J. Chim. phys.*, 1955, **52**, 666.

reaction might follow a different course and give products not obtainable by normal means; indeed, previous work [2] had suggested that chlorination induced by γ-rays might follow a different course from the photochemical reaction. We have therefore made a parallel study of radiation- and free-radical-induced chlorination and bromination. Other results of this investigation have been briefly published elsewhere.[3]

Experimental.—Materials. Chlorine was obtained commercially. The first 50% of the gas obtained from the cylinder was discarded to remove any less-dense impurities present initially. The remaining chlorine was passed through calcium chloride and used without further purification. *N*-Bromosuccinimide was recrystallised from hot water and dried under a high vacuum. Its purity determined iodometrically was better than 99%. Nitration-grade toluene was used for the chlorinations. It was fractionally distilled, and the distillate shown to be pure within the limits of gas-phase chromatographic analysis. Benzyl chloride, which was purified by distillation immediately before use, contained traces of benzylidene chloride and chlorotoluene. For the chlorinations " AnalaR " carbon tetrachloride was treated with chlorine, in the absence of oxygen, washed, dried, and distilled before use. *cyclo*Hexene was distilled before use. Other materials were of " AnalaR " quality where possible.

Radiation sources. A " Hanovia " lamp fitted with a glass filter was the source of ultraviolet light. Only wavelengths longer than 3000 Å, and mainly 3660 Å, were emitted. All the incident ultraviolet photons were absorbed in the solution. γ-Irradiations were carried out in a 500-curie cobalt-60 source emitting 1·17 and 1·33 Mev photons, doses being measured with the ferrous sulphate dosimeter, G_{ferric} being assumed [4] to be 15·5. A 2Mev, 0·5 kw Van de Graaff accelerator was used as source of fast electrons. The beam could be scanned over various distances.

Results.—Chlorination. Identical solutions containing an aromatic compound (in excess over chlorine) were prepared for random irradiation with ultraviolet light, γ-rays, or fast electrons, or for thermal reaction in the absence of radiation. All reagents were distilled under a high vacuum into a vessel cooled in liquid nitrogen, and this was allowed to warm to the reaction temperature in the dark. Negligible reaction occurred during the preparation of solutions. Irradiation was continued until all the chlorine had been consumed, solutions being stirred throughout ultraviolet irradiation. The products were then analysed. Hydrogen chloride was measured titrimetrically except when acetic acid was present; it was then measured gravimetrically. Organic products of boiling point below 270° were estimated by gas-phase chromatography. Oily droplets were always found in the reaction vessel. They had the characteristic smell of hexachloro*cyclo*hexane derivatives, and their formation accounts for the excess of chlorine consumed over substitution products formed. Typical results obtained at 18° are shown in the Table. We have also found that at 0° ultraviolet light gives the same distribution of products as γ-rays. From the absorbed dose in the γ-ray experiments the *G*-values were calculated to be of the order of ten thousand, thus proving a chain reaction.

Chlorination of toluene at 18°.
All solutions (10 *ml.*) *contained* 5·5 *mmoles of chlorine initially.*

Solvent	Initiation	Reaction time (min.)	Hydrogen chloride (mmoles)	Benzyl chloride (mmoles)	Chlorotoluene (mmoles)
None	Thermal	720	3·2	0·7	1·6
None	Ultraviolet	0·75	3·8	2·6	0·3
None	γ-Rays	6	3·4	2·9	0·1
None	Fast electrons	<0·02	3·3	3·4	0·2
CCl_4	Ultraviolet	4	4·1	2·5	0
CCl_4	γ-Rays	70	4·3	2·3	0
$CH_3{\cdot}CO_2H$	Ultraviolet	2	3·0	2·7	0·7
$CH_3{\cdot}CO_2H$	γ-Rays	10	3·7	3·0	0·8

In contrast to previous findings [2] we found that benzyl chloride was as readily chlorinated by use of γ-rays as by ultraviolet light, the main products being hydrogen chloride and benzylidene chloride. The chlorination proceeded at about a tenth of the rate of that of toluene. It may be that the lack of chlorination in the previous experiments was due to the

[3] Cox and Swallow, *Chem. and Ind.*, 1956, 1277.
[4] Haybittle, Saunders, and Swallow, *J. Chem. Phys.*, 1956, **25**, 1213.

presence of traces of impurities. Toluene could be chlorinated with γ-rays in benzyl chloride as solvent, the rate being about the same as in acetic acid.

Bromination with N-*bromosuccinimide.* The best conditions for the radiation-catalysed bromination of *cyclo*hexane were the same as those described by Ford and Waters for chemical catalysis.[5] Bromination was achieved by irradiating a suspension of *N*-bromosuccinimide (10·8 g., 0·06 mole) in boiling *cyclo*hexane (64·7 ml., 0·6 mole) with an electron beam (20 μA), scanned over 20 cm. A product, b. p. 65°/18 mm. (4·4 g.), was shown to be *cyclo*hexyl bromide (46% calculated on the bromo-imide) by conversion into *cyclo*hexylmercuric bromide, m. p. and mixed m. p. 148°. The energy yield was $G = 40$. Higher energy yields could be obtained at lower percentage conversions, but irradiation in the cold or at higher dose rates gave lower energy yields.

*cyclo*Hexene could not be brominated by using radiation under Ford and Waters's conditions because of the rapid occurrence of a dark reaction. However bromination could be achieved in the cold. A suspension of *N*-bromosuccinimide (10·8 g., 0·06 mole) in a mixture of *cyclo*hexene (10·7 ml., 0·106 mole) and carbon tetrachloride (13·3 ml.) was stirred and irradiated in absence of air (20 μA; 20 cm. scan). A product, b. p. 70—72°/30 mm. (6·0 g.), was shown to be 3-bromo*cyclo*hexene (58% calculated on the bromo-imide) by hydrolysis with cold aqueous sodium hydrogencarbonate to *cyclo*hex-2-en-1-ol which in turn was identified bycon version into *cyclo*hex-2-enyl naphthylcarbamate, m. p. and mixed m. p. 156·5°. The energy yield was $G = 450$. Lower yields were obtained at higher dose rates, or when oxygen was present during irradiation, or when carbon tetrachloride was not used.

Discussion.—Our chlorinations show that providing temperature, solvent and concentration of solute are kept the same, there is no significant difference between the products of ultraviolet- and of radiation-catalysed reactions. Moreover, alteration of solvent alters the distribution of products and approximate reaction time equally for the two modes of initiation. Hence the difference between the γ-ray experiments of Harmer, Anderson, and Martin [2] and previous ultraviolet experiments is attributable to differences in reaction conditions. Evidently the propagation steps in the two chain reactions are the same under identical conditions, even though the initial acts differ. The results contrast with the thermal reaction, which gave a different distribution of products. This is probably because the thermal reaction is an ionic one, catalysed by hydrogen chloride,[6] rather than a free-radical chain reaction.

Similarly, when bromination could be carried out under the appropriate conditions, as with *cyclo*hexane, our yields with radiation as catalyst do not differ significantly from those reported by Ford and Waters, using dimethyl αα′-azo*iso*butyrate.[5] Also, in the bromination of toluene previously reported [3] the principal product was benzyl bromide, formed in the same yield as in the reaction catalysed by free radicals. Bromotoluene would have been expected for an ionic reaction.[7]

The authors thank M. Allen and P. J. Horner for technical assistance, W. H. T. Davison and M. McKeown for analyses, and the Chairman of Tube Investments Ltd. for permission to publish this work.

TUBE INVESTMENTS RESEARCH LABORATORIES,
HINXTON HALL, CAMBRIDGE. [*Received, April,* 24th, 1958.]

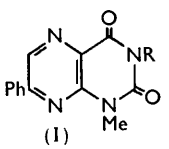
[5] Ford and Waters, *J.*, 1952, 2240.
[6] Schonken, Le Page, and Jungers, *Bull. Soc. chim. France*, 1957, 1394.
[7] Schmid, *Helv. Chim. Acta*, 1946, **29**, 1144.

752. *Pteridine Derivatives. Part VI.* Aminolysis of a Pteridone.*

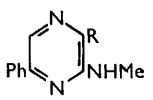
By G. P. G. Dick, D. Livingston, and H. C. S. Wood.

The ease with which *N*-alkylpteridones can be degraded with dilute alkali is well known,[1,2] but the effect of other nucleophilic reagents has not been investigated. Taylor[3] has reported that hydroxypteridines on treatment with a variety of amines undergo cleavage to give *N*-substituted pyrazinecarboxyamides. We now describe briefly the action of amines on 1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxo-7-phenylpteridine (I; R = Me).

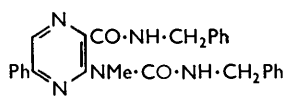
It has already been shown[2] that compound (I; R = Me) gives a quantitative yield of 3-methylamino-5-phenylpyrazine-2-carboxymethylamide (II; R = CO·NHMe) when refluxed with ethanolic 0·1N-potassium hydroxide, the initial attack by hydroxyl ion taking place at $C_{(2)}$ and being followed by ring opening. On treatment of the pteridone (I; R = Me) with alcoholic ammonia at 210°, cleavage takes place to give 3-methylamino-5-phenylpyrazine-2-carboxyamide (II; R = $CO·NH_2$). Similarly the pteridone (I; R = Me) in refluxing hydrazine hydrate gave the carboxyhydrazide (II; R = $CO·NH·NH_2$). The structure of these degradation products was established in each case by synthesis from the known 3-methylamino-5-phenylpyrazine-2-carboxylic acid (II; R = CO_2H) *via* the methyl ester (II; R = CO_2Me). The initial attack by an amine takes place at $C_{(4)}$ giving the appropriately *N*-substituted pyrazinecarboxyamide directly. The alternative mechanism, which involves attack at $C_{(2)}$ to give the methylamide (II; R = CO·NHMe) followed by aminolysis of the amide group, is excluded by the observation that the methylamide (II; R = CO·NHMe) is not attacked by ammonia under the appropriate conditions.



(I)



(II)



(III)

Benzylamine, which was effective for the cleavage of hydroxypteridines,[3] does not attack the pteridone (I; R = Me) even under drastic conditions. Study of Stuart models indicates that this is probably due to steric hindrance, the methyl group on $N_{(3)}$ preventing the approach of the bulky benzylamine molecule. Support for this suggestion was obtained by treating the pteridone (I; R = H) with benzylamine: cleavage took place to give a pyrazine derivative to which we assign structure (III), analogous to the intermediate compound obtained by Taylor[3] on treatment of a 2 : 4-dihydroxypteridine with benzylamine. None of the expected simple carboxybenzylamide (II; R = $CO·NH·CH_2Ph$) could be detected in paper chromatograms of the reaction mixture.

The pteridone (I; R = H) was prepared by treatment of the carboxyamide (II; R = $CO·NH_2$) with ethyl chloroformate to give 2-cyano-3-(*N*-ethoxycarbonyl-*N*-methylamino)-5-phenylpyrazine[4] which readily cyclised to give the pteridone (I; R = H) when refluxed with sodium methoxide.

Experimental.—*3-Methylamino-5-phenylpyrazine-2-carboxyamide.* (*a*) 1 : 2 : 3 : 4-Tetrahydro-1 : 3-dimethyl-2 : 4-dioxo-7-phenylpteridine (0·25 g.), dry ethanol (20 c.c.), and liquid ammonia (5 c.c.) were heated in a steel bomb at 210° for 20 hr. The resulting yellow solution was filtered, and the filtrate evaporated *in vacuo* to an orange-yellow solid. This was extracted

* Part V, *J.*, 1957, 4157.

[1] Albert, Brown, and Wood, *J.*, 1956, 2066; Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 2380.
[2] Dick, Wood, and Logan, *J.*, 1956, 2131.
[3] Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1651.
[4] Cf. Pfleiderer, *Chem. Ber.*, 1956, **89**, 1148.

with boiling light petroleum (b. p. 60—80°; 4 × 30 c.c.), and the combined extracts were evaporated and crystallised from chloroform–light petroleum to give *3-methylamino-5-phenylpyrazine-2-carboxyamide* (0·168 g., 79%) as fine yellow needles, m. p. 188—189° (Found: C, 63·1; H, 4·9; N, 24·7. $C_{12}H_{12}ON_4$ requires C, 63·1; H, 5·3; N, 24·6%).

3-Methylamino-5-phenylpyrazine-2-carboxymethylamide [2] was recovered unchanged when treated with ammonia under the above conditions.

(*b*) Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate (0·13 g.) and saturated ethanolic ammonia (5 c.c.) were heated in a sealed tube at 125° for 5 hr. The cooled mixture was filtered, and the filtrate evaporated to dryness *in vacuo*. The residue, recrystallised from chloroform–light petroleum, gave the carboxyamide (0·1 g., 80%), m. p. and mixed m. p. 188—189°.

3-Methylamino-5-phenylpyrazine-2-carboxyhydrazide. (*a*) The pteridine (I; R = Me) (0·5 g.) and 85% hydrazine hydrate (15 c.c.) were refluxed for 6 hr. The deep yellow needles which separated on cooling were collected, washed with water and methanol, and dried. Recrystallisation from chloroform–methanol gave *3-methylamino-5-phenylpyrazine-2-carboxyhydrazide* (0·37 g., 80%) as fluffy yellow needles, m. p. 215—216·5° (Found: C, 59·3; H, 5·2; N, 28·9. $C_{12}H_{13}ON_5$ requires C, 59·3; H, 5·4; N, 28·8%).

(*b*) Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate (0·1 g.) and 85% hydrazine hydrate (2 c.c.) were refluxed for 30 min., then cooled, and the carboxyhydrazide (0·08 g., 80%) was collected and recrystallised as above (m. p. and mixed m. p. 216—217°).

Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate. 3-Methylamino-5-phenylpyrazine-2-carboxylic acid [2] (85 mg.) in dry boiling methanol (200 c.c.) was treated with dry hydrogen chloride for 10 min., and the solution was refluxed for a further 2 hr. The mixture was concentrated *in vacuo* to 10 c.c., water (10 c.c.) was added, and, on chilling, the *methyl ester* (80 mg., 93%) separated as fine yellow needles, m. p. 134—135° (Found: C, 64·3; H, 5·2; N, 17·3. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%).

2-Cyano-3-(N-ethoxycarbonyl-N-methylamino)-5-phenylpyrazine. 3-Methylamino-5-phenylpyrazine-2-carboxyamide (1·1 g.) and redistilled ethyl chloroformate (30 c.c.) were refluxed for 20 hr. The solution was evaporated to dryness *in vacuo*, ethanol (50 c.c.) was added, and the solution again taken to dryness. Extraction of the residue with light petroleum (b. p. 60—80°; 50 c.c.), and refrigeration of the extract gave the *nitrile* (1·02 g., 75%) as thick colourless blades, m. p. 66—67° (Found: C, 63·9; H, 4·5; N, 20·0. $C_{15}H_{14}O_2N_4$ requires C, 63·8; H, 5·0; N, 19·9%). The infrared spectrum (in CCl_4) shows bands at 2247 (CN) and 1739 $cm.^{-1}$ (ester).

1 : 2 : 3 : 4-Tetrahydro-1-methyl-2 : 4-dioxo-7-phenylpteridine. The above nitrile (0·64 g.) in methanol (10 c.c.) was added to a solution from sodium (0·5 g.) in methanol (20 c.c.), and the mixture was heated on the steam-bath for 1 hr. The resulting solution was taken to dryness *in vacuo*, water (25 c.c.) was added, and the pH was adjusted to *ca.* 4 with dilute hydrochloric acid. The pale yellow solid which separated was collected and recrystallised from 80% formic acid, to give the *pteridone* (0·23 g., 34%) as yellow needles, m. p. 349—350° (Found: C, 61·3; H, 3·5; N, 21·8. $C_{13}H_{10}O_2N_4$ requires C, 61·4; H, 4·0; N, 22·0%).

3-(N-Benzylcarbamoyl-N-methylamino)-5-phenylpyrazine-2-carboxybenzylamide. The pteridone (0·15 g.) was refluxed for 8 hr. with redistilled benzylamine (3 c.c.). On cooling, fine yellow needles (50 mg.) separated which recrystallised readily from benzylamine, to give *3-(N-benzylcarbamoyl-N-methylamino)-5-phenylpyrazine-2-carboxybenzylamide*, m. p. 255—256° (Found: C, 71·7; H, 4·8. $C_{27}H_{25}O_2N_5$ requires C, 71·8; H, 5·5%). The infrared spectrum (in $CHCl_3$) shows a strong carbonyl absorption band at 1660 and a medium band at 1700 $cm.^{-1}$ (cf. ref. 3).

3-Methylamino-5-phenylpyrazine-2-carboxybenzylamide. Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate (0·22 g.) and benzylamine (5 c.c.) were refluxed together for 30 min. The solution was taken to dryness *in vacuo*, and re-evaporated several times with ethanol to remove traces of benzylamine. Crystallisation of the residue from aqueous methanol gave the *benzylamide* (0·15 g., 52%) as yellow needles, m. p. 96—97° (Found: C, 71·8; H, 5·7; N, 17·6. $C_{19}H_{18}ON_4$ requires C, 71·7; H, 5·7; N, 17·6%).

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753. *The Vapour Density and Dissociation Pressure of Phosphorus Pentabromide.*

By G. S. Harris and D. S. Payne.

There is no record of the vapour density of phosphorus pentabromide though, in text-books, it is generally assumed that the vapour is more or less dissociated into phosphorus tribromide and bromine: $PBr_5 \rightleftharpoons PBr_3 + Br_2$. To obtain information about the extent of dissociation, vapour density was measured over a wide temperature range (65—180°). The apparent molecular weight of the vapour remains constant, within experimental error, at half the calculated molecular weight of phosphorus pentabromide, corresponding to complete dissociation.

The dissociation pressure of solid phosphorus pentabromide was also re-measured (from 19·0° to 75·0°) (data were reported by Prideaux [1] and van Driel and Gerding [2]). The plot of $\log_{10} p$ (mm.) *versus* $1/T°$ (abs.) in the range 32·5—75·0° was reproducibly straight and described by $\log_{10} p = -2895{\cdot}7T^{-1} + 10{\cdot}1713$ (by the method of least squares). From this and the complete dissociation of the vapour at 65·0°, it follows that between 32·5° and 75° the solid-vapour equilibrium is of the type Solid $\rightleftharpoons$ Gas + Gas for which the equilibrium constant (K_P) is $K_P = \frac{1}{4}P^2$ [P is the total pressure, atm.). Consequently, for phosphorus pentabromide, $\log_{10} K_P$ (atm.) $= 5791{\cdot}4T^{-1} + 13{\cdot}979$ which gives 26·50 kcal. mole^{-1} as the heat of dissociation of solid phosphorus pentabromide to gaseous phosphorus tribromide and bromine (van Driel and Gerding's data yield a value of 27·12 kcal. mole^{-1}). From 19·0° to 32·5° the vapour pressures tended upward, possibly owing to incomplete dissociation of the vapour at these lower temperatures. Vapour density was not measured in this range because of the reduced sensitivity of the method at very low pressures.

Experimental.—Good commercial phosphorus pentabromide was recrystallised from pure nitrobenzene and washed with dry ether, the last traces of which were removed in a current of dry nitrogen. The compound was manipulated in a dry-box.

Dissociation pressures. These were measured by a static method in an all-glass system incorporating a spoon-gauge with an optical lever which was used as a null-meter. Pressures were read on a cathetometer as a difference in mercury levels in a wide-tube manometer.

The constant-volume section of the apparatus (containing the compound) was kept at constant temperature in an electrically heated oil-bath. The dissociation pressure was recorded only after solid–vapour equilibrium was set up (after 1—2 hr.); values for ascending and descending temperatures are grouped together in Table 1. The mean deviation of values of $\log_{10} p$ is 0·017318.

Table 1. *Dissociation pressure of solid phosphorus pentabromide.*

Temp. (° c)	76·0	72·9	65·2	65·1	61·8	61·0	59·9	57·9	57·5	55·8	55·0
P (mm.) ...	75·85	68·16	43·14	38·90	34·00	30·45	26·70	26·57	26·06	23·29	22·99
Temp. (° c)	52·0	49·0	49·0	48·0	44·4	41·9	40·7	39·0	36·0	35·1	32·4
P (mm.) ...	18·19	13·09	14·94	14·29	10·97	9·72	8·26	7·80	6·06	6·30	5·30

Vapour density. A similar apparatus was used, but the constant-volume part was enlarged by the attachment of a bulb (*ca.* 100 ml.). Small samples of the compound were used so that it would vaporise completely. The temperature of the thermostat was raised in stages and the corresponding pressures noted. The temperature at which complete vaporisation occurred was observed visually and from the abrupt levelling-off of the pressure–temperature graph. Beyond this point and up to 180° the pressure at various temperatures was recorded and in this region the P–T graph was straight with a small positive slope. From these measurements and the mass and volume of vapour, the apparent molecular weight M (app.) (calc. for PBr_5 : M, 430·6), and hence the degree of dissociation (α) of phosphorus pentabromide were calculated.

[1] Prideaux, *J.*, 1909, **95**, 445.
[2] van Driel and Gerding, *Rec. Trav. chim.*, 1941, **60**, 869.

Table 2 summarises the results of two experiments with 0·0595 g. and 0·1697 g. samples of phosphorus pentabromide in volumes of 144·8 ml. and 143·4 ml. respectively. The estimated error is about 1%.

TABLE 2. *State of phosphorus pentabromide vapour.*

Temp. (° c) ...	65·0	77·5	90·0	100·0		110·0	122·5	137·5	150·0	165·0	180·0
P (mm.)	40·0	41·5	43·1	44·4		131·5	135·9	141·1	145·3	150·2	155·1
M (app.)	216·9	216·8	216·1	215·7		215·1	214·9	214·9	215·0	215·4	215·7
α (%)	98·5	98·6	99·2	99·6		100·2	100·3	100·4	100·2	99·9	99·6

We thank the Department of Scientific and Industrial Research for an award (to G. S. H.).

THE UNIVERSITY, GLASGOW, W.2. [*Received, April 28th*, 1958.]

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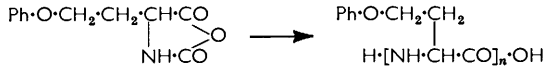
754. *Synthesis of Poly-O-phenyl-DL-homoserine.*

By MAX FRANKEL and Y. KNOBLER.

N-CARBOXY-*O*-PHENYL DL-HOMOSERINE ANHYDRIDE, m p. 105°, has been prepared by us from the benzyloxycarbonyl derivative of *O*-phenyl-DL-homoserine[1] or, preferably, directly[2] from the amino-acid and carbonyl chloride. Polymerisation of the *N*-carboxy-anhydride was effected by melting it under a vacuum.



The hard brittle polymers obtained were soluble in dimethylformamide or in chloroform and precipitated on addition of ether. Glacial acetic acid caused partial dissolution, leaving the higher-melting fractions of greater chain-length undissolved; from the soluble, lower-melting fractions, polymers of shorter chain-length were recovered on precipitation with water.

The poly-*O*-phenyl-DL-homoserine preparations obtained from the *N*-carboxy-anhydride synthesised by action of carbonyl chloride on the free amino-acid had greater average chain-length, as shown by their amino-nitrogen content. They exhibited pronounced fibre-forming properties. The fractions not soluble in hot glacial acetic acid had the greatest ability of extension on stretching. Fractions of an average molecular weight of 21,000—26,000, corresponding to an average chain-length of 120—150 units, were obtained.

Experimental.—M. p.s were determined in a Fisher–Johns apparatus.

N-Benzyloxycarbonyl-O-phenyl-DL-homoserine. Benzyl chloroformate (7·3 g.) and 4N-sodium hydroxide (15 ml.) were dropped with stirring simultaneously into a solution of *O*-phenyl-DL-homoserine (7·8 g.) in 2N-sodium hydroxide (30 ml.) at 0° during ½ hr.; stirring was continued for ½ hr. at 0° and for 1 hr. without cooling. Washing the mixture with toluene and precipitation with 18% hydrochloric acid gave an oil which solidified at 0°. The solid recrystallised from ether–light petroleum or ethyl acetate–light petroleum, giving *N*-benzyloxycarbonyl-*O*-phenyl-DL-homoserine (9·2 g., 70%), m. p. 118° (Found: C, 65·4; H, 5·7; N, 4·25. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·25%).

N-Carboxy-O-phenyl-DL-homoserine anhydride. (*a*) *N*-Benzyloxycarbonyl-*O*-phenyl-DL-homoserine (6·6 g.) was dissolved in dry ether (200 ml.) and treated with phosphorus pentachloride (4·1 g.) in the usual manner. The anhydride solidified under light petroleum or over phosphoric oxide. Recrystallised from ether–light petroleum, dioxan–light petroleum, or ethyl acetate–light petroleum it gave the N-*carboxy-anhydride* (3·6 g., 81%) as a white powder, m. p. 105°. It decomposes slowly in cold water; a ninhydrin reaction is detectable only after boiling. After prolonged storage in water it gave a gradually deepening biuret colour, positive

[1] Fischer and Blumenthal, *Ber.*, 1907, **40**, 106; Painter, *J. Amer. Chem. Soc.*, 1947, **69**, 232.
[2] Fuchs, *Ber.*, 1922, **55**, 2943; Levy, *Nature*, 1950, **165**, 152; Farthing and Reynolds, *Nature*, 1950, **165**, 647.

also in pyridine solution [Found: C, 60·0; H, 5·2; N (Kjeldahl), 6·1; N (Van Slyke), 6·2. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%].

(*b*) The *N*-carboxy-anhydride was prepared by passing dry carbonyl chloride at 40—60° (bath) through a suspension of *O*-phenyl-DL-homoserine (3·9 g.) in dioxan. Recrystallised as under (*a*), the anhydride (3 g., 70%) had m. p. 105—106°. It evolved carbon dioxide when heated in water, giving then a positive ninhydrin and a slight biuret reaction (positive biuret reaction in pyridine solution) [Found: C, 59·6; H, 5·1; N (Kjeldahl), 6·2; N (Van Slyke), 6·2%].

Poly-O-phenyl-DL-homoserine. Freshly prepared recrystallised *N*-carboxy-anhydride (4·6 g.) was gradually heated at an initial pressure of 0·5—1 mm. At 100—110° (bath) the substance melted with evolution of gas, causing rise in pressure. The bath temperature was kept during 1 hr. at 100—110°, then raised during 2 hr. to 135°, causing steady evolution of gas and finally vigorous foaming. As no gas evolution occurred by increasing the bath temperature at this point, the substance was kept for 1 hr. at 100° (bath) at the initial pressure.

Poly-*O*-phenyl-DL-homoserine, synthesised from the anhydride obtained by method (*b*), was washed with hot (100°) glacial acetic acid and subsequently with dry ether. Dried over phosphoric oxide *in vacuo* it became plastic at 260—280° and decomposed at 280—300°. After evaporation of its chloroform solution, the soft mass remaining could be cold drawn to form elastic fibres, which on loss of solvent became rigid. The average chain-length of this fraction varied between 120 and 150 units [Found: C, 67·6; H, 6·3; N (Kjeldahl), 7·9; N (Van Slyke), 0·065, 0·06, 0·05, 0·05. $(C_{10}H_{11}O_2N)_{120}$ requires C, 67·7; H, 6·2; N, 7·9; N (amino), 0·66. $(C_{10}H_{11}O_2N)_{150}$ requires N (amino), 0·053%].

The fraction precipitated from chloroform–ether and dried *in vacuo* (P_2O_5) became plastic at 225—250° and decomposed at 250—280°. After softening with chloroform it also could be cold drawn to form elastic fibres, but less readily than in the former case. Its average chain-length varied from 40 to 70 units [Found: C, 67·3; H, 6·1; N (Kjeldahl), 7·9; N (Van Slyke), 0·2, 0·15, 0·15, 0·11. $(C_{10}H_{11}O_2N)_{50}$ requires N (amino), 0·16%].

Poly-*O*-phenyl-DL-homoserine obtained by heating *in vacuo* (as above) of the anhydride prepared *via* the chloride of the *N*-benzyloxycarbonyl-acid had shorter average chain-length after undergoing the same fractionation. The fraction insoluble in glacial acetic acid (100°) was a polymer of 20—30 units, semiplastic at 150—200°, melting at 200—230°, decomposing above 250°. It softened after addition of chloroform; its ability to be stretched was very limited [Found: C, 66·5; H, 6·0; N (Kjeldahl), 7·6; N (Van Slyke), 0·3, 0·3, 0·5. $(C_{10}H_{11}O_2N)_{20}$ requires N (amino), 0·4%). Substances precipitated from dimethylformamide–ether or from chloroform–ether were of an average chain-length 10—20 units; the fraction soluble in glacial acetic acid and precipitated with water was composed (average) of 10 units, having lower melting ranges and without fibre-forming properties.

All fractions (2—2·5 g.) gave an intensive biuret colour.

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755. *The Heat of Formation of Trimethylgallium.*

By P. A. FOWELL and C. T. MORTIMER.

THE thermochemistry of alkyl and aryl compounds of the Group II metals zinc, cadmium, and mercury has been studied in some detail and information is also available for the alkyl compounds of the Group IV metals tin and lead.[1] Comparatively little is known about the metal–carbon bond in the alkyls of the Group III metals gallium, indium, and thallium. The heat of reaction at 55° of liquid trimethylgallium with iodine in benzene solution, which has now been measured, yields $\Delta H_f°(GaMe_3, liq.) = -14·5 \pm 8$ kcal./mole. The *mean* dissociation energy of the Ga–C bond in trimethylgallium is 56·7 ± 4 kcal./mole.

Experimental.—Materials. Trimethylgallium was prepared by refluxing, under nitrogen, gallium (Light and Co., 99·95% pure), dimethylmercury (b. p. 91·0—91·2°/748 mm.), and a

[1] For references, see Mortimer, *J. Chem. Educ.*, 1958, in the press.

trace of methylmercury chloride as catalyst.[2] After 24 hr. the vapour temperature fell and trimethylgallium (4 g.) was taken from the top of a 6 in. Fenske column during 24 hr. (b. p. 56·0°/764 mm.; Kraus and Toonder [3] give 55·7 ± 0·2°/762 mm.). It was redistilled *in vacuo* and sealed in thin, weighed glass phials.

Gallium tri-iodide (Johnson Matthey and Co.), analysed by the 8-hydroxyquinoline method,[4] was 99·9% pure.

Iodine and benzene were " AnalaR "; the latter was washed four times with concentrated sulphuric acid, then with sodium hydrogen carbonate, and dried by refluxing it with calcium hydride in a stream of nitrogen (trimethylgallium reacts vigorously with both oxygen and water).

Methyl iodide was distilled through an 18 in. Fenske column, and redistilled *in vacuo* before use.

Calorimeter. This was a narrow-necked 400 ml. Dewar vessel, immersed in an oil-bath at 60°, and contained 350 ml. of Shell Diala BX oil, initially at 55°. The oil covered a stirrer (480 r.p.m.), a shielded thermistor, a calibration heater, and a reaction vessel. The last contained 25 ml. of a solution of iodine in benzene, saturated with nitrogen, and a phial of trimethylgallium which was broken to start the reaction. The usual temperature rise was about 0·25°. The energy equivalent of the calorimeter was determined electrically by substitution.

Units. All heat quantities are given in units of the thermochemical calorie, 1 cal. ≡ 4·1840 abs. joule. The reactions were carried out at 55°.

Results. According to Wiberg, Johannsen, and Stecher [5] the reaction

$$GaMe_3,liq. + 3I_2,c. \longrightarrow GaI_3,c. + 3MeI,liq. \quad . \quad . \quad . \quad . \quad . \quad (1)$$

proceeds slowly, but quantitatively, at room temperature, and more quickly at 60°. At room temperature, both in benzene and ether, only two-thirds of the theoretical quantity of iodine reacted immediately:

$$GaMe_3,liq. + 2I_2,soln. \longrightarrow MeGaI_2,soln. + 2MeI,soln. \quad . \quad . \quad . \quad . \quad (2)$$

At 55° in benzene, with a molar ratio of trimethylgallium to iodine of 1 : 7, about 70% of the iodine required by eqn. (1) reacted, and with a ratio of 1 : 20 the amount was 87%. Of the total heat of reaction, about 80% was evolved in the first 4 min., and after 45 min., heat continued to be evolved at the rate of 0·3% per min. The temperature of the contents of the calorimeter at this time was arranged to be near the " equilibrium " temperature, so that heat transfer was small. About 45 min. after the reaction had started, the reaction vessel was removed from the calorimeter and cooled, and the contents were analysed for iodine. It was estimated that the error in the measurement of the heat of reaction was not more than ±0·5 kcal./mole and that in determining the percentage of reaction ±1%.

To produce a high percentage of reaction required a large excess of iodine, which, however, has a comparatively low solubility (~0·6M) in benzene. Thus, high percentages could only be achieved by using small amounts of trimethylgallium, with consequently small temperature changes. Attempts to increase the temperature change by using more benzene involved the difficulties of stirring a closed system at 55° or of keeping an open system free from oxygen and moisture, and the errors introduced outweighed the advantage.

The observed heats of reaction, $\Delta H_{obs.}$, in benzene, together with the amount of iodine consumed as a percentage of that required by reaction (1), are tabulated. A plot of $\Delta H_{obs.}$

$GaMe_3$ (g.)	0·3383	0·1052	0·1262	0·0529	0·0950	0·1178	0·0488	0·0877
Iodine consumed (%)	70·7	71·4	72·6	78·0	80·6	82·5	86·6	87·0
$-\Delta H_{obs.}$ (kcal./mole)	48·5	47·5	49·1	50·9	54·4	54·0	53·5	57·3

against iodine consumed (%), when extrapolated to 66·7% of iodine consumed, gives $\Delta H_{(2)} = -46·4 \pm 1$ kcal./mole for the heat of reaction (2) and to 100% of iodine consumed gives $\Delta H_{(3)} = -60·5 \pm 2$ kcal./mole for the heat of the reaction

$$GaMe_3,liq. + 3I_2,soln. \longrightarrow GaI_3,soln. + 3MeI,soln. \quad . \quad . \quad . \quad . \quad (3)$$

[2] Coates, *J.*, 1951, 2003.
[3] Kraus and Toonder, *Proc. Nat. Acad. Sci. U.S.A.*, 1933, **19**, 292.
[4] Moeller and Cohen, *Analyt. Chem.*, 1950, **22**, 686.
[5] Wiberg, Johannsen, and Stecher, *Z. anorg. Chem.*, 1943, **251**, 114.

There was no heat change when a phial containing liquid methyl iodide was broken in iodine–benzene at 55°. Gallium tri-iodide dissolved slowly in benzene containing both dissolved iodine and methyl iodide with no measurable heat change. The heat of solution in benzene [6]

$$I_2,c. \longrightarrow I_2,soln.\ \Delta H_{I_2 soln.} = +4{\cdot}25 \text{ kcal./mole at } 25°$$

gives $$\Delta H_{(1)} = \Delta H_{(3)} + 3\Delta H_{I_2 soln.} = -47{\cdot}8 \pm 2 \text{ kcal./mole}$$

The heat change when methylgallium di-iodide dissolves in benzene containing dissolved iodine and methyl iodide was not measured. However, if it is zero, as for gallium tri-iodide, then the heat, $\Delta H_{(4)}$, of the reaction

$$GaMe_3,liq. + 2I_2,c. \longrightarrow MeGaI_2,c. + 2MeI,liq. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

given by $\Delta H_{(4)} = \Delta H_{(2)} + 2\Delta H_{I_2 soln.}$ is $-37{\cdot}9 \pm 1$ kcal./mole.

Discussion.—The heats of formation of liquid trimethylgallium and crystalline methylgallium di-iodide can be calculated from the $\Delta H_{(1)}$ and $\Delta H_{(4)}$ by incorporating $\Delta H_f°(GaI_3,c.) = -51{\cdot}2$ kcal./mole [7] and $\Delta H_f°(MeI,liq.) = -3{\cdot}7 \pm 2$ kcal./mole (values of the heat of formation of methyl iodide have been critically considered by Hartley, Pritchard, and Skinner,[8] and Skinner [9] has suggested that this value is the " best ").

Too few specific-heat data are available to calculate $\Delta H_{(1)}$ and $\Delta H_{(4)}$ at 25° from the value at 55°. However, assuming these to be the same at 25°, we calculate $\Delta H_f°(GaMe_3,liq.) = -14{\cdot}5 \pm 8$ kcal./mole, and incorporating the heat of vaporisation, $\Delta H_{vap.} = 7{\cdot}8$ kcal./mole,[3] we find $\Delta H_f°(GaMe_3,g.) = -6{\cdot}7 \pm 8$ kcal./mole.

Taking our value for $\Delta H_f°(GaMe_3,liq.)$ and that already given for $\Delta H_f°(MeI,liq.)$, we find $\Delta H_f°(MeGaI_2,c.) = -45{\cdot}0 \pm 5$ kcal./mole.

The *mean* bond dissociation energy $\bar{D}(Ga–C)$, for the dissociation

$$GaMe_3,g \div Ga,g. + 3Me,g.$$

can be calculated from the relation

$$3\bar{D}(Ga–C) = \Delta H_f°(Ga,g.) + 3\Delta H_f°(Me,g.) - \Delta H_f°(GaMe_3,g.)$$

Using our value for $\Delta H_f°(GaMe_3,g.)$, together with $\Delta H_f°(Me,g.) = 32{\cdot}6 \pm 1$ kcal./mole [10] and $\Delta H_f°(Ga,g.) = 65{\cdot}6 \pm 0{\cdot}5$ kcal./mole,[11] we find $\bar{D}(Ga–C) = 56{\cdot}7 \pm 4$ kcal./mole.

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UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE. [*Received, April 29th,* 1958.]

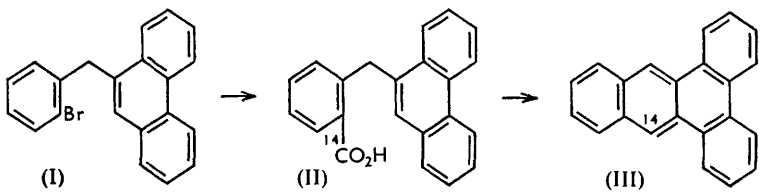
[6] Hartley and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 621.
[7] Klemm, Tilk, and Jacobi, *Z. anorg. Chem.*, 1932, **207**, 187.
[8] Hartley, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 1019.
[9] Skinner, personal communication.
[10] Mortimer, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1952, **48**, 220
[11] Speiser and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 1469.

756. ^{14}C-*Labelled Polycyclic Aromatic Hydrocarbons. Part IV.*[1] *A Synthesis of* 1 : 2-3 : 4-*Dibenz*[9-^{14}C]*anthracene and the Attempted Synthesis of* 1 : 2-3 : 4-5 : 6-*Tribenzanthracene.*

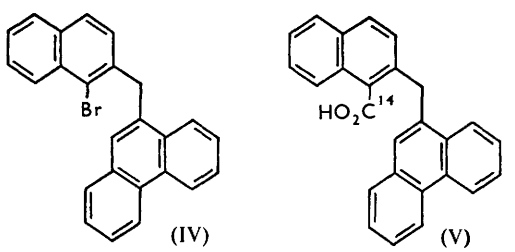
By E. A. Evans.

In continuation of the investigation of new improved synthetic routes to ^{14}C-labelled polycyclic aromatic hydrocarbons,[2] this Note records the synthesis, from $^{14}CO_2$ in three steps only, of the pentacyclic weakly carcinogenic hydrocarbon 1 : 2-3 : 4-dibenz[9-^{14}C]-anthracene.[3] An unsuccessful attempt to prepare 1 : 2-3 : 4-5 : 6-tribenzanthracene [4] is also recorded.

The route chosen was similar to that described in previous papers in this series.[2] The intermediate bromide (I) was prepared by reaction of *o*-bromobenzaldehyde with 9-phenanthrylmagnesium bromide, followed by reduction of the secondary alcohol with red phosphorus and iodine in glacial acetic acid. In a Grignard reaction with $^{14}CO_2$ the



bromide (I) gave 75—98% yields of the acid (II), identical with that prepared by Clemmensen reduction of 9-*o*-carboxybenzoylphenanthrene [5] made from 9-phenanthrylmagnesium bromide and phthalic anhydride. Attempts to cyclise 9-*o*-carboxybenzoylphenanthrene with concentrated sulphuric acid or with phosphoric oxide in tetralin gave unidentifiable brown amorphous solids, even under mild conditions.[6] However, the acid (II) was readily cyclised in hydrogen fluoride and was then reduced to the hydrocarbon (III) with zinc dust in sodium hydroxide. The overall yield from $^{14}CO_2$ was approximately 30%.



The dibenzanthracene was best purified by crystallisation from glacial acetic acid and, as in the case of 1 : 2-5 : 6-dibenzanthracene,[1] only partial purification could be effected by chromatography on alumina in benzene. The radiochemical purity determined by dilution analysis was greater than 98%.

An attempt to prepare the bromo-compound (IV) by reaction of 1-bromo-2-naphthaldehyde with 9-phenanthrylmagnesium bromide followed by reduction of the

[1] Part III, *J.*, 1957, 2796.
[2] Catch and Evans, *J.*, 1957, 2796, and preceding papers.
[3] Cf. Elsevier's "Encyclopaedia of Organic Chemistry," Vol. XIV, p. 450; Clar and Lombardi, *Ber.*, 1932, **65**, 1411.
[4] Fieser and Dietz, *Ber.*, 1929, **62**, 1827.
[5] Bergmann and Berlin, *J.*, 1939, 493.
[6] Cf. Graebe and Peter, *Annalen*, 1905, **340**, 259; Weizmann, Bergmann, and Bergmann, *J.*, 1935, 1367.

alcohol gave a bromo-compound containing approximately 50% of the expected bromine content. The compound formed a Grignard reagent with difficulty, and on carboxylation gave a poor yield of the acid (V) (?). Attempted cyclisation of this acid (V) with anhydrous hydrogen fluoride, followed by reduction with zinc dust in 5N-sodium hydroxide, gave only traces of unidentifiable brown solids.

Experimental.—M. p.s were observed on a Kofler block and are corrected. Ultraviolet absorption measurements were made on ethanol solution by a Unicam S.P. 500 instrument. Grignard reactions were conducted in dry oxygen-free nitrogen.

9-o-*Bromobenzylphenanthrene.* *o*-Bromobenzaldehyde (9 g.) in anhydrous ether (25 ml.) was added dropwise to 9-phenanthrylmagnesium bromide (prepared from 9-bromophenanthrene 13 g., magnesium 1·5 g., and iodine one crystal) in ether (20 ml.) and benzene (20 ml.). After 1 hour's stirring of the mixture at room temperature excess of saturated aqueous ammonium chloride was added and the ether–benzene layer separated. The aqueous layer was extracted with ether (2 × 20 ml.), the organic layers were combined, and the solvents removed under reduced pressure. The residual dark brown oil was dissolved in glacial acetic acid (150 ml.), then iodine (3 g.), red phosphorus (3 g.), and water (15 ml.) were added and the mixture was heated under reflux for 27 hr. The solution was cooled to 0° and filtered, most of the acetic acid neutralised with 10% sodium hydroxide solution, and the whole extracted with ether until the extracts were colourless (*ca.* 3 × 100 ml.). The combined extracts were washed with 10% sodium hydroxide solution (2 × 100 ml.), then water (2 × 50 ml.), and dried (Na_2SO_4–Na_2CO_3). The ether was removed under reduced pressure and the residual brown solid was chromatographed on alumina in 3 : 1 light petroleum (b. p. 40—60°)–benzene, giving 9-o-*bromobenzylphenanthrene* (7 g., 41·5%), which crystallised in colourless plates [from benzene–light petroleum (b. p. 40—60°)], m. p. 134—135° (Found: C, 72·8; H, 4·6; Br, 22·1. $C_{21}H_{15}Br$ requires C, 72·7; H, 4·3; Br, 23·0%).

9-o-[^{14}C]*Carboxybenzylphenanthrene.* A Grignard reagent was prepared from 9-*o*-bromobenzylphenanthrene (3·5 g.), magnesium (0·25 g.), iodine (1 crystal), and methyl iodide (1—2 drops) in ether (15 ml.) and benzene (15 ml.) under reflux in 2—3 hr. $^{14}CO_2$ (generated from barium [^{14}C]carbonate, 1·773 g., 0·9 mc, with concentrated sulphuric acid) was condensed into the above Grignard reagent in a closed vacuum-system by freezing in liquid nitrogen. The solution was stirred for 30 min. at room temperature and the acid isolated with ether. The ether was extracted with 2N-sodium hydroxide (*ca.* 5 × 20 ml.), and the combined alkaline extracts on acidification at 0° with concentrated hydrochloric acid gave the carboxylic acid (2·128 g., 76%), m. p. 188—190°. This crystallised in plates (from benzene–*cyclo*hexane), m. p. 189—190° (Found: C, 85·0; H, 5·1. Calc. for $C_{22}H_{16}O_2$: C, 84·6; H, 5·1%) (Bergmann and Berlin [5] give m. p. 197°). The m. p. of the acid was undepressed on admixture with the acid, m. p. and mixed m. p. 189°, prepared as below.

In other carboxylations, yields from 75 to 98% (based on CO_2) of the acid were obtained by increasing the excess of Grignard reagent.

High-activity preparation. $^{14}CO_2$ (from barium [^{14}C]carbonate, 0·394 g., 20 mc) was condensed into a Grignard reagent prepared from 9-*o*-bromobenzylphenanthrene (1 g.), magnesium (0·1 g.), iodine (1 crystal), and methyl iodide (1—2 drops) in ether (15 ml.) and benzene (10 ml.). Isolation of the acid as above gave the [^{14}C]oic acid (0·5 g., 80%), m. p. 188—190°.

1 : 2-3 : 4-*Dibenz*[9-^{14}C]*anthracene.* The acid (2·128 g., *ca.* 100 μc/mmole) was left in anhydrous hydrogen fluoride (20—25 ml.) for 1 hr. at room temperature with frequent stirring, and then poured on ice. The product was filtered off and heated under reflux for 10 hr. with zinc dust (15 g., previously activated with copper sulphate solution), 5N-sodium hydroxide (100 ml.), and toluene (50 ml.). After cooling, the toluene layer was separated and the aqueous layer extracted with benzene (2 × 50 ml.). The excess of zinc dust was washed with hot benzene (3 × 10 ml.), and the combined benzene and toluene layers were dried (Na_2SO_4). Organic solvents were distilled off under reduced pressure, leaving a yellow solid which crystallised in straw-coloured needles (0·8 g., 42%) (from glacial acetic acid), m. p. 199—201°. (Clar and Lombardi [3] give m. p. 205°.)

The specific activity of the hydrocarbon was 92·4 μc/mmole of radiochemical purity 99% (by dilution analysis, see Part III), and the overall radiochemical yield from $^{14}CO_2$ was 29%. Only traces of acid were recovered from the alkaline liquors of the reduction.

In the high-activity preparation on a 2-mmolar scale, carrier dibenzanthracene was added

before the material was purified. From acid (0·5 g., *ca.* 16 mc) was obtained 1 : 2-3 : 4-dibenz[9-^{14}C]anthracene (2·87 mc) at 2·79 mc/mmole. The radiochemical purity was found to be 98% by dilution analysis.

9-o-*Carboxybenzoylphenanthrene*. 9-Phenanthrylmagnesium bromide (prepared from 9-bromophenanthrene 14 g., magnesium 1·5 g., and iodine 1 crystal) in ether (20 ml.) and benzene (30 ml.) was added dropwise to phthalic anhydride (7 g.) in benzene (200 ml.). A canary-yellow complex was formed and the mixture was heated under reflux for 2 hr. The solution was cooled and poured into excess of ice-cold 2N-sulphuric acid. The organic layer was separated, the aqueous layer was extracted with 2N-sodium carbonate (5 × 50 ml.), and the alkaline extracts were acidified with concentrated hydrochloric acid. The acid (15 g.) was filtered off, dried in *vacuo*, and crystallised from xylene or benzene–*cyclo*hexane in plates, m. p. 176—177° (Weizmann, Bergmann, and Bergmann [6] give m. p. 174—175°). Lower yields of the acid were obtained when the phthalic anhydride was added to the Grignard reagent.

Amalgamated zinc was prepared by shaking for 5 min. a mixture of zinc wool (50 g.), mercuric chloride (5 g.), water (150 ml.), and concentrated hydrochloric acid (5 ml.). The solution was decanted and the following added to the zinc: water (50 ml.), concentrated hydrochloric acid (120 ml.), toluene (100 ml.), and 9-*o*-carboxybenzoylphenanthrene (5 g.). The solution was heated under reflux for 30 hr. and concentrated hydrochloric acid (30 ml.) was added every 6 hr. for the first 18 hr. After cooling, the toluene layer was separated and the aqueous layer extracted with ether (3 × 50 ml.), the zinc being washed each time. The combined organic layers were extracted with 2N-sodium hydroxide (5 × 20 ml.), and the acid was precipitated from the alkaline extracts with concentrated hydrochloric acid at 0°. Crystallisation from benzene–*cyclo*hexane gave plates (3 g.), m. p. 189—190°, undepressed on admixture with the 9-*o*-carboxybenzylphenanthrene prepared as above.

Carrier 1 : 2-3 : 4-*dibenzanthracene*. Cyclisation of 9-*o*-carboxybenzylphenanthrene (3 g.) with anhydrous hydrogen fluoride (50 ml.), followed by reduction with zinc dust in 5N-sodium hydroxide, as described above, gave 1 : 2-3 : 4-dibenzanthracene (1·2 g., 45%), m. p. 202—203°, pale yellow needles (from acetic acid); $\lambda_{max.}$ 265° (ε 66,200), 2750 (ε 98,600), 2860 (ε 130,300), and 3200 Å (ε 7170).

Attempted preparation of 9-(1-*bromo*-2-*naphthylmethyl*)*phenanthrene*. 1-Bromo-2-naphthaldehyde (12 g.) in benzene (150 ml.) was added dropwise to 9-phenanthrylmagnesium bromide (prepared from 9-bromophenanthrene, 14 g., etc.) in ether (20 ml.) and benzene (20 ml.). The mixture was heated under reflux for 4 hr. Working up the product as for the homologue (above), and reducing the secondary alcohol with red phosphorus and iodine, gave a product which was chromatographed on alumina in 1 : 1 benzene–light petroleum (b. p. 40—60°), giving a substance (6 g.) as plates, m. p. 155—157° (this m. p. could not be raised) (Found: C, 82·7; H, 5·1; Br, 12·1%).

9-(2-*Carboxy*-1-*naphthylmethyl*)*phenanthrene* (?). Carbon dioxide (from barium carbonate 0·394 g., generated with concentrated sulphuric acid) was condensed into the Grignard reagent prepared from the above bromo-compound (1 g.), magnesium (0·1 g.), iodine (1 crystal), and methyl iodide (1—2 drops) in benzene (15 ml.) and ether (10 ml.). Working up and isolation of the acid as above gave an *acid* (0·5 g.), m. p. 236—238°, which crystallised from benzene or benzene–*cyclo*hexane in plates (0·13 g.), m. p. 243—244° after several recrystallisations (Found: C, 85·6; H, 5·25. $C_{26}H_{18}O_2$ requires C, 86·2; H, 5·0%). From the neutral fraction was obtained a substance (0·4 g.), m. p. 175° (from ethanol) (Found: C, 93·5; H, 5·7. Calc. for $C_{25}H_{18}$: C, 94·3; H, 5·7%), which may be impure 9-(2-naphthylmethyl)phenanthrene.

In hydrogen fluoride this acid was largely destroyed.

The author thanks Dr. W. P. Grove and Dr. J. R. Catch for their interest, and the Atomic Energy Authority for the award of a Harwell fellowship.

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757. p-*Hydrazophenetole.*

By M. Khalifa and A. A. Abo-Ouf.

Reduction of *o*-azophenetole with alcoholic ammonium sulphide to the hydrazo-derivative and failure of the *para*-isomer to undergo a similar change have been reported,[1] though later success in reducing *p*-azophenetole was claimed [2] but without experimental details. In numerous attempts we failed to reduce the *para*-compound by this reagent.

Khalifa and Linnell [3] found that lowering the electron-density on the azo-group favours its reduction to the hydrazo-stage by zinc. In conformity we find that *p*-azoxyphenetole is reduced by zinc in ethanolic potassium hydroxide approx. twice as fast as *p*-azophenetole. The resulting *p*-hydrazophenetole has the m. p. reported earlier.[2]

Experimental.—p-*Hydrazophenetole.* To *p*-azophenetole (0·1 g.), dissolved in stirred, boiling alcohol (10 ml.), zinc dust (1 g.) was added, followed by 30% alcoholic potassium hydroxide (12 drops per min.) until the mixture was no longer coloured. The filtrate was rapidly cooled in ice. The hydrazo-compound separated in needles, m. p. 118—119°.

The above reduction was complete in about 30 min. With the azoxy-compound it required only 15 min.

We thank Professor Y. M. Abou-Zeid of this Faculty for facilities.

Organic Chemistry Department, Faculty of Pharmacy,
Cairo University. [*Received, April 9th,* 1958.]

[1] Schmitt and Möhlau, *J. prakt. Chem.*, 1878, **18**, 202.
[2] Kinzel, *Arch. Pharm.*, 1891, **229**, 351.
[3] Khalifa, Thesis, London, 1955.

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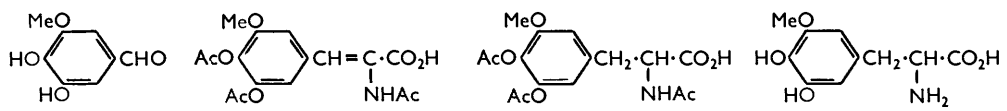
758. β-(3 : 4-*Dihydroxy*-5-*methoxyphenyl*)*alanine.*

By P. Smith.

β-(3 : 4-Dihydroxy-5-methoxyphenyl)alanine (IV), a compound of possible physiological interest in view of its relation to β-(3 : 4-dihydroxyphenyl)alanine, adrenaline, and mescaline, has been synthesised from 3 : 4-dihydroxy-5-methoxybenzaldehyde (I). Condensation of the latter with acetylglycine and mild hydrolysis of the crude azlactone gave the acetamidocinnamic acid (II), catalytic hydrogenation of which afforded the triacetyl derivative (III) from which the hydrochloride of the required amino-acid was obtained by hydrolysis with dilute hydrochloric acid.



(I) (II) (III) (IV)

Previous preparations of the aldehyde (I) by alkaline hydrolysis of 5-bromovanillin [1] require the use of an autoclave which was not available. However 5-iodovanillin undergoes the required hydrolysis at atmospheric pressure and was itself readily prepared by iodination of vanillin under mild alkaline conditions.

Experimental.—Nitrogen analyses were performed by a semimicro-Kjeldahl technique on samples containing about 2 mg. of nitrogen.

[1] Bradley, Robinson, and Swarzenbach, *J.*, 1930, 793.

5-Iodovanillin. Iodine (12·6 g.) was added in four portions during 30 min. to a rapidly stirred suspension of vanillin (7·5 g.) in water (200 ml.) containing sodium hydrogen carbonate (5 g.) and potassium iodide (10 g.). Stirring was continued for 3 hr. and the mixture left overnight. The filtered product was washed with dilute sodium thiosulphate and water and dried at 45° (11·8 g., m. p. 175°). Crystallised from aqueous ethanol, it had m. p. 180° (Bougault and Robin [2] give m. p. 180°).

3 : 4-*Dihydroxy-5-methoxybenzaldehyde* (I). A mixture of 5-iodovanillin (26·7 g.), copper powder (10 g.), and aqueous sodium hydroxide (20% w/v; 270 ml.) was refluxed for 4 hr. After cooling, acidification with concentrated hydrochloric acid, addition of a little sodium sulphite, and filtration, the solution was extracted continuously with ether. Usually the gradual separation of solid promoted extensive emulsification and complete extraction of the product became impracticable, but on one occasion 15 g. of light-grey material, m. p. 120—127°, were obtained. Crystallisation from ethyl acetate–chloroform (charcoal) gave the aldehyde (11·0 g.) as almost colourless platelets, m. p. 128—131°, raised to 132° by recrystallisation from ethyl acetate (Bradley, Robinson, and Swarzenbach [1] give m. p. 132—134°).

α-*Acetamido*-3 : 4-*diacetoxy-5-methoxycinnamic acid* (II). A mixture of the above aldehyde (5 g.), acetylglycine (3·75 g.), fused sodium acetate (2·4 g.), and acetic anhydride (22·5 ml.) was heated at 100° for 90 min. The yellow crystalline azlactone obtained after cooling and gradual addition of water (45 ml.) was filtered off and washed with acetic acid (33% v/v) and then with water; this was dissolved in hot dioxan (20 ml.) and kept at 100° for 15 min. while water (20 ml.) was gradually added. The hot solution was treated with charcoal (2 g.) and hot water added until the supernatant liquid was pure yellow. After filtration the solution gradually deposited yellow crystals (3·6 g.), m. p. 181—184° after being dried (P_2O_5). Crystallisation from ethanol–benzene–light petroleum (b. p. 60—80°) with charcoal treatment gave the *acetamidocinnamic acid* as colourless prisms, m. p. 184—185° (Found: N, 3·8. $C_{16}H_{17}O_8N$ requires N, 4·0%).

N-*Acetyl*-β-(3 : 4-*diacetoxy-5-methoxyphenyl*)*alanine* (III). Absorption occurred slowly when the acetamidocinnamic acid (3·52 g.) was shaken in ethanol–ethyl acetate with hydrogen in the presence of 5% palladium–charcoal (1·0 g.). After 24 hr., filtration and evaporation afforded a gum which solidified when triturated with ethyl acetate. The *product* (3·1 g., m. p. 180—182°) after recrystallisation from ethanol–benzene had m. p. 190—192° (Found: N, 3·85. $C_{16}H_{19}O_8N$ requires N, 3·95%).

β-(3 : 4-*Dihydroxy-5-methoxyphenyl*)*alanine* (IV). The triacetyl derivative (1·3 g.) was refluxed under nitrogen with N-hydrochloric acid (15 ml.) for 3 hr., and the residue after evaporation (0·95 g., m. p. 225—230° decomp.) dried *in vacuo* (P_2O_5; KOH). Crystallisation from methanol–ether afforded the *amino-acid hydrochloride*, m. p. 228—229° (decomp.) (Found: N, 5·25. $C_{10}H_{14}O_5NCl$ requires N, 5·3%), some of which was converted into the free *amino-acid monohydrate* by passing an aqueous solution through a short column of the weakly basic resin Deacidite " E " (acetate form); the residue after evaporation of the filtrate and washings was crystallised from water (m. p. 222—224°) (Found: N, 5·75. $C_{10}H_{13}O_5N,H_2O$ requires N, 5·7%). Its weight (123 mg.) was unchanged after desiccation (P_2O_5) for 18 hr. at 10 mm., but it subsequently lost 8 mg. (calc., 9 mg.) when heated at 100°/0·1 mm. for 2 hr. These properties resemble those of 2 : 5-dihydroxyphenylalanine monohydrate.[3]

The author thanks Mrs. G. A. Hill and Mr. J. Ratcliffe for experimental assistance and the Director-General of Medical Services, Royal Air Force, for permission to publish this work.

ROYAL AIR FORCE INSTITUTE OF AVIATION MEDICINE,
FARNBOROUGH, HANTS.

[*Received, May 9th,* 1958.]

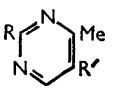
[2] Bougault and Robin, *Compt. rend.*, 1921, **172**, 452.
[3] Neuberger, *Biochem. J.*, 1948, **43**, 599.

759. *Pyrimidines. Part III.* The Synthesis and Some Reactions of 5-Ethynylpyrimidines.*

By R. HULL.

BIOLOGICAL and chemical [1] interests in acetylenic compounds have been mainly confined to aliphatic compounds. Few ethynyl heterocyclic compounds have been synthesised. This paper describes the preparation of two 5-ethynylpyrimidines.

5-Acetyl-4-methyl-2-phenylpyrimidine [2] (I) was converted into the 5-1′-chlorovinylpyrimidine (II) by phosphorus pentachloride, which with alcoholic potassium hydroxide gave 5-ethynyl-4-methyl-2-phenylpyrimidine (III).



(I): R = Ph, R′ = COMe
(II): R = Ph, R′ = CCl:CH$_2$
(III): R = Ph, R′ = C:CH

(IV): R = Ph, R′ = CH:CH·S·COMe
(V): R = NMe$_2$, R′ = COMe
(VI): R = NMe$_2$, R′ = C:CH

The infrared spectrum (0·05 mm. molten layer) of compound (III) contains bands at 2·9 and 4·65 μ which can be attributed to the 5-acetylenic group. Compound (III) formed a silver salt and was converted into the monoadduct (IV) by thioacetic acid.[3] These observations confirm structure (III).

The 2-dimethylamino-analogue (VI) was prepared by a similar series of reactions from the 5-acetylpyrimidine (V).

Experimental.—*5-1′-Chlorovinyl-4-methyl-2-phenylpyrimidine.* Phosphorus pentachloride (37 g.) was added slowly to a stirred warm solution of 5-acetyl-4-methyl-2-phenylpyrimidine [2] (37 g.) in dry benzene (200 ml.), and the whole was heated under reflux during 2 hr. The cooled mixture was poured into ice and water (250 ml.), and the aqueous phase neutralised with sodium carbonate. After 30 minutes' stirring the benzene layer was separated and the aqueous phase re-extracted with benzene. The extracts were combined and dried and excess of solvent was removed by distillation. The main fraction of the residue (36 g.) distilled from a bath at 145°/0·1 mm. to give the *chlorovinylpyrimidine* as a pale brown oil (Found: C, 67·8; H, 5·1; N, 12·7; Cl, 14·9. $C_{13}H_{11}N_2Cl$ requires C, 67·7; H, 4·8; N, 12·2; Cl, 15·4%).

5-Ethynyl-4-methyl-2-phenylpyrimidine. A solution of 5-1′-chlorovinyl-4-methyl-2-phenylpyrimidine (3·3 g.) in alcohol (15 ml.) was added to potassium hydroxide (2·4 g.) in 95% alcohol (15 ml.), and the whole was heated under reflux during 2 hr. and then evaporated to dryness. Water was added to the residue and the product was extracted with ether. The extract was dried and evaporated and the residue (2 g.) distilled at 150—155° (bath-temp.)/0·18 mm., giving the *ethynylpyrimidine* which set to needles. Recrystallisation from light petroleum (b. p. 40—60°) gave the product as needles, m. p. 64—65°, $\lambda_{max.}$ (in MeOH) 280 mμ (ε 26,500), shoulder at 287 mμ, $\lambda_{min.}$ 235 mμ (ε 3100) (Found: C, 80·0; H, 5·3; N, 14·6. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·15; N, 14·45%); the infrared spectrum, determined on a 0·05 mm. molten layer, showed bands centred about 2·9 and 4·65 μ. Ammoniacal silver nitrate in 50% aqueous alcohol (prepared from 0·36 g. of silver nitrate) was added slowly to a stirred solution of 5-ethynyl-4-methyl-2-phenylpyrimidine (0·4 g.) in warm ethanol (7 ml.). The *silver salt* was collected and washed with water and alcohol (Found: Ag, 34·4. $C_{13}H_9N_2Ag,0·5H_2O$ requires Ag, 34·8%).

2-(4-Methyl-2-phenyl-5-pyrimidylvinyl) thiolacetate. Thioacetic acid (0·8 g.) and 5-ethynyl-4-methyl-2-phenylpyrimidine (2·04 g.) were mixed and heated gently to a single phase. After 7 days the mixture had set to a mass of yellow needles. The *product* distilled as a pale yellow oil from a bath at 130/0·1 mm., setting to yellow needles (Found: C, 66·3; H, 5·1; N, 10·6. $C_{15}H_{14}ON_2S$ requires C, 66·65; H, 5·2; N, 10·4%).

5-Acetyl-2-dimethylamino-4-methylpyrimidine. Dimethylguanidine sulphate [4] (6·8 g.) and ethoxymethyleneacetylacetone (7·85 g.) were added to a cooled solution of sodium (1·15 g.) in

* Part II, *J.*, 1957, 4845.

[1] Bu'Lock, *Quart. Rev.*, 1956, **10**, 371; Johnson, *Sci. Progr.*, 1954, **42**, 469.
[2] Mitter and Bardhan, *J.*, 1923, 2179.
[3] Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619.
[4] Phillips and Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1756.

alcohol (20 ml.), and the whole was heated under reflux during 2 hr. After cooling, the mixture was filtered, the filtrate was evaporated to dryness, and the solids were combined; inorganic material was removed by washing with water. The *acetylpyrimidine* (7 g.) recrystallised from water in needles, m. p. 56—57° (Found: C, 60·1; H, 7·7; N, 23·0. $C_9H_{13}ON_3$ requires C, 60·35; H, 7·3; N, 23·45%). The *semicarbazone* crystallised from alcohol in needles, m. p. 226—227° (Found: C, 51·1; H, 7·7. $C_{10}H_{16}ON_6$ requires C, 50·9; H, 6·8%).

5-1′-Chlorovinyl-2-dimethylamino-4-methylpyrimidine. 5-Acetyl-2-dimethylamino-4-methylpyrimidine (2·58 g.) and phosphorus pentachloride (3 g.) were heated under reflux in benzene (30 ml.) during 2 hr. The cooled mixture was poured, with stirring, into ice-water and neutralised with sodium carbonate. The benzene layer was separated and combined with further benzene extracts of the aqueous phase and dried. After removal of solvent the residue (1·9 g.) distilled from a bath at 100°/0·08 mm., to give the *chlorovinylpyrimidine* as a colourless oil (Found: C, 55·4; H, 6·3; N, 21·0; Cl, 18·1. $C_9H_{12}N_3Cl$ requires C, 54·7; H, 6·1; N, 21·25; Cl, 18·1%).

2-Dimethylamino-5-ethynyl-4-methylpyrimidine. 5-1′-Chlorovinyl-2-dimethylamino-4-methylpyrimidine (14·7 g.) in alcohol (50 ml.) was heated with potassium hydroxide (12·5 g.) in 95% alcohol (80 ml.) under reflux during 2 hr., then evaporated to dryness. Water was added and the product extracted with ether. After removal of solvent the *ethynylpyrimidine* (9·4 g.) distilled at 80—84°/0·1 mm. as a dark red oil (Found: C, 65·3; H, 6·6; N, 24·7. $C_9H_{11}N_3,0·25H_2O$ requires C, 65·25; H, 6·8; N, 25·35%). The compound did not give a Beilstein test for halogen and formed a silver salt with ammoniacal silver nitrate.

The author thanks Mr. M. St. C. Flett for the infrared, and Dr. J. M. Pryce for the ultraviolet, absorption determinations.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION,
ALDERLEY PARK, MACCLESFIELD, CHESHIRE. [*Received, May 15th*, 1958.]

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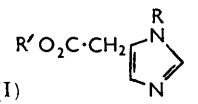
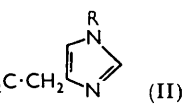
760. *Synthesis of* 1-β-D-*Ribofuranosyl*-4(5)-*glyoxalinylacetic Acid, a Metabolite of Histamine.*

By J. BADDILEY, J. G. BUCHANAN, D. H. HAYES, and P. A. SMITH.

AMONG the metabolites which appear in the urine of rats and mice after interperitoneal injection of histamine [1] is a ribofuranosyl derivative of 4-glyoxalinylacetic acid [2-4] (I or II; R = ribofuranosyl, R′ = H). The compound was characterised as the crystalline hydrochloride and shown to give the acid (I; R = R′ = H) and ribose on acidic [2,4] or enzymic [3] hydrolysis. The glycoside consumed one mol. of periodate. Two structural features were not decided by the degradative evidence: (i) the relative positions of the ribosyl group and the acetic acid side chain and (ii) the anomeric configuration of the ribosyl group. This paper describes a synthesis which establishes the configuration of the ribosyl linkage.


(I)


(II)

The mercurichloride salt [5] of methyl 4-glyoxalinylacetate was condensed with tri-*O*-benzoyl-β-D-ribofuranosyl chloride [6] in boiling xylene. The product was debenzoylated

[1] Schayer, *J. Biol. Chem.*, 1952, **196**, 469; Mehler, Tabor, and Bauer, *ibid.*, 1952, **197**, 475; Tabor, Mehler, and Schayer, *ibid.*, 1953, **200**, 605; Bouthillier and Goldner, *Arch. Biochem. Biophys.*, 1953, **44**, 251; Karjala and Turnquest, *J. Amer. Chem. Soc.*, 1955, **77**, 6358; Schayer and Karjala, *J. Biol. Chem.*, 1956, **221**, 307.
[2] Karjala, *J. Amer. Chem. Soc.*, 1955, **77**, 504.
[3] Tabor and Hayaishi, *ibid.*, p. 505.
[4] Karjala, Turnquest, and Schayer, *J. Biol. Chem.*, 1956, **219**, 9.
[5] Cf. Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650, and subsequent papers.
[6] Kissman, Pidacks, and Baker, *ibid.*, 1955, **77**, 18.

and the methyl ester group hydrolysed with acid. Isolation of the ribosyl compound was effected by ion-exchange chromatography, finally as the hydrochloride. Comparison with the natural compound, kindly given to us by Dr. H. Tabor, showed the two to be indistinguishable in melting point, infrared spectrum, and R_F values in a number of solvent systems, as well as in their behaviour on acid hydrolysis.

Reaction of a tri-*O*-acetyl- or tri-*O*-benzoyl-ribofuranosyl halide with mercury salts [5] yields only the β-anomer in all cases so far studied. This establishes the β-configuration of the natural compound.

Experimental.—Methyl 4-glyoxalinylacetate. Crude 4-glyoxalinylacetic acid hydrochloride (42·8 g.), prepared by acid hydrolysis of the cyanide,[7] was heated under reflux with methanol (200 c.c.) for 1 hr. Paper chromatography showed almost complete esterification. The solution was evaporated to dryness, the residue dissolved in water, and the solution basified with sodium hydrogen carbonate, then evaporated. The dry residue was extracted with warm ethyl acetate (8 × 50 c.c.) and the filtered extracts were evaporated to an oil (28·5 g., 75%). The oil was dissolved in methanol (50 c.c.), and a solution of oxalic acid dihydrate (27·0 g.) in methanol (75 c.c.) added. The *oxalate*, m. p. 164—168°, crystallised as plates (24·5 g.). Recrystallised from water–acetone or methanol it had m. p. 173—174° (Found: N, 12·4. $C_8H_{10}O_6N_2$ requires N, 12·1%). It gave a *picrate*, m. p. 167·5—168·5°, lemon-yellow prisms from ethanol (Found: C, 38·7; H, 3·0; N, 18·8. $C_{12}H_{11}O_9N_5$ requires C, 39·0; H, 3·0; N, 19·0%).

Mercurichloride salt of methyl 4-glyoxalinylacetate. The above oxalate (2·3 g.) was dissolved in water (25 c.c.), and the solution basified with sodium carbonate, saturated with ammonium chloride, and extracted with ethyl acetate (8 × 20 c.c.). The extract was dried (Na_2SO_4) and evaporated to an oil (1·12 g., 80%). Paper chromatography showed only one spot. The free ester was dissolved in 50% aqueous methanol (40 c.c.), and a solution of sodium hydroxide (0·392 g.) in methanol (20 c.c.) added at 10°, followed by mercuric chloride (2·68 g.) in methanol (60 c.c.). The precipitate was centrifuged immediately and washed with portions (100 c.c.) of methanol, water, methanol, and ether. The white amorphous solid (3·5 g., 93%) was virtually free from 4-glyoxalinylacetic acid as shown by chromatography.

1-β-D-*Ribofuranosyl*-4(5)-*glyoxalinylacetic acid.* The above mercury salt (3·5 g.) was powdered and suspended in dry sulphur-free xylene (200 c.c.). " Hyflo Supercel " (7 g.) was added and xylene (50 c.c.) was distilled off at atmospheric pressure. A solution of tri-*O*-benzoylribofuranosyl chloride [from the 1-*O*-acetyl compound (4·71 g.)] in xylene (56 c.c.) was added and the mixture was boiled, with stirring, for 1 hr. The suspension was filtered while hot and the residue washed with xylene (20 c.c.). The filtrate was evaporated to a gum (4·17 g.). By crystallisation from methanol 1-*O*-acetyl-2 : 3 : 5-tri-*O*-benzoyl-β-D-ribose (0·28 g.) was obtained. The remaining material was debenzoylated with sodium methoxide (from 0·075 g. of sodium) in methanol (total volume 160 c.c.). When debenzoylation was complete (paper chromatography) the solution was filtered and evaporated to dryness and the residue dissolved in 4N-hydrochloric acid (40 c.c.). Extraction with chloroform removed methyl benzoate and benzoic acid. The aqueous solution was evaporated to dryness and to the residue (1·6 g.) was added concentrated hydrochloric acid (25 c.c.). The mixture was boiled under reflux for 10 min., cooled, and filtered (charcoal), and the filtrate evaporated to dryness several times with water to give a gummy residue (1·0 g.). This material (0·5 g.) was dissolved in water (75 c.c.) and the pH adjusted to 4. It was chromatographed on a Dowex-50(X8) (H^+) column (200—400 mesh; 33 × 2 cm.). Separation from glyoxalinylacetic acid was carried out by gradient elution, using water and 2·9N-hydrochloric acid. 25 c.c. Fractions were collected and the riboside was detected by using the periodate–Schiff spray.[8] The appropriate fractions were evaporated to dryness, the residue dissolved in water, and the pH made slightly alkaline with sodium hydroxide. The riboside was adsorbed on a column of Dowex-1(X2) acetate (22 × 2·5 cm.), and the column washed with water. The riboside was eluted with 2N-acetic acid, being detected as before.[8] The appropriate fractions were evaporated to dryness and the *ribosylglyoxaline hydrochloride* (96 mg.) obtained by crystallisation from dilute hydrochloric acid–acetone. It had m. p. 177—179°, undepressed on admixture with the natural compound,

[7] Pyman, *J.*, 1911, **99**, 668.
[8] Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

and $[\alpha]_D^{22}$ −52·6° (*c* 0·5 in MeOH) (Found: C, 40·6; H, 5·3; N, 9·8. $C_{10}H_{15}O_6N_2Cl$ requires C, 40·7; H, 5·1; N, 9·5%). The ribosyl compound consumed 0·98 mol. of sodium metaperiodate.[9] The infrared spectrum (KBr disc) was identical with that of the natural compound. When it was hydrolysed with 0·1N-hydrochloric acid at 145° for 5 hr.[2,4] glyoxalinylacetic acid and ribose were formed.

Paper chromatography. Whatman No. 4 paper was used. Glyoxalines lacking a nitrogen-substituent were detected by the Pauly spray,[10] ribose by aniline phthalate,[11] and ribosides by the periodate–Schiff spray.[8] Solvents: (A) *n*-propyl alcohol (75)–ammonia (*d* 0·88) (25); (B) *n*-propyl alcohol (6)–ammonia (*d* 0·88) (3)–water (1); (C) *n*-butyl alcohol (4)–acetic acid (1)–water (5) (upper layer).

	R_F in solvents		
	A	B	C
4-Glyoxalinylacetic acid	—	0·64	0·32
Methyl 4-glyoxalinylacetate	—	0·91	0·59
1-Ribosyl-4(5)-glyoxalinylacetic acid	0·21	0·52	0·26
Ribose	—	0·54	0·30

We thank the Nuffield Foundation and the British Empire Cancer Campaign for financial assistance.

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[*Received, May 15th,* 1958.]

[9] Dixon and Lipkin, *Analyt. Chem.*, 1954, **26**, 1092.
[10] Dent, *Biochem. J.*, 1947, **41**, 240.
[11] Partridge, *Nature*, 1949, **164**, 443.

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761. *The Reduction of* N-*Phenylhydroxylamine with Lithium Aluminium Hydride.*

By M. L. BURSTALL and M. S. GIBSON.

REDUCTION of nitrobenzene,[1] nitrosobenzene,[2] and azoxybenzene[1] with lithium aluminium hydride has in each case been reported to give azobenzene. The binuclear products of reduction of nitrobenzene in aqueous media seem generally to be attributed to the formation and subsequent reactions of *N*-phenylhydroxylamine.[3] It was of interest, therefore, to determine the course of reduction of this compound with lithium aluminium hydride. The products are azobenzene and aniline in nearly equimolar amounts. The non-formation of aniline in the reductions reported previously[1,2] has been confirmed.

The absence of aniline from the reduction products of nitrobenzene and nitrosobenzene may be taken to suggest that *N*-phenylhydroxylamine is not formed as a reaction intermediate in either case. If *N*-phenylhydroxylamine is formed transiently and undergoes preferential reduction, a mechanism must be postulated for the complete removal of the aniline so formed, *e.g.*, condensation with nitrosobenzene; but if it condenses with nitrosobenzene (giving azoxybenzene), the absence of aniline in the reduction products is accommodated.

It may be noted that the reduction of *N*-phenylhydroxylamine (to aniline and azobenzene) can be explained on the basis of its disproportionation to aniline and azoxybenzene before reduction.[3]

Experimental.—Nitrobenzene was distilled before use; nitrosobenzene, azoxybenzene, and *N*-phenylhydroxylamine were freshly prepared and crystallised.

N-Phenylhydroxylamine (3·1 g.) in ether (25 ml.) was added to lithium aluminium hydride (4·0 g.) in boiling ether (100 ml.) during 10—15 min. After a further ½ hr., excess of reagent was destroyed with ethyl acetate. A little water was added, and the granular precipitate

[1] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738.
[2] Weil, Prijs, and Erlenmeyer, *Helv. Chim. Acta*, 1953, **36**, 142.
[3] Sidgwick, " Organic Chemistry of Nitrogen," Oxford, 1949, pp. 252 *et seq.*

was filtered off and washed with ether. The combined filtrate and washings were dried ($MgSO_4$) and evaporated, and the red residue (2·4 g.) was chromatographed on alumina, yielding (i) azobenzene [1·33 g., eluted with light petroleum (b. p. 60—80°)–benzene], (ii) and (iii) gummy fractions (0·1 g., 0·1 g., eluted with benzene and ether respectively), and (iv) aniline (0·7 g., eluted with chloroform). Azobenzene formed orange-red leaflets (from ethanol), m. p. and mixed m. p. 68° (Found: C, 78·2; H, 5·4. Calc. for $C_{12}H_{10}N_2$: C, 78·0; H, 5·5%). Fraction (iv) was identified as aniline from its infrared spectrum, and by conversion into acetanilide, plates (from water), m. p. and mixed m. p. 113—114°.

In like manner, nitrobenzene, nitrosobenzene, and azoxybenzene gave azobenzene in yields of 85% (lit., 84%), 72% (lit., 69%) and 96% (lit., 99%) respectively; in the first two cases, chromatographic fractions following azobenzene afforded some gum. No aniline was detected in these reductions.

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BASIC RESEARCH DEPARTMENT, THOMAS HEDLEY & CO., LTD.,
NEWCASTLE UPON TYNE, 1. [*Received, May 20th*, 1958.]

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762. *Formation and Properties of a Dipyridine–Germanium Tetrachloride Adduct.*

By E. W. ABEL.

DESPITE considerable interest [1] in the reactions of germanium tetrachloride for the preparation of substitution products of germane, there has been little investigation of co-ordination of the tetrahalides. Thomas and Southwood [2] stated that tertiary amines were without action on germanium tetrachloride; Trost,[3] however, reported formation of $GeCl_4(NEt_3)_4$, and Johnson and Sidwell recorded [4] the compound $GeI_4(NEt_3)_5$.

We have found that an excess of pyridine with germanium tetrachloride produces a dipyridine–germanium tetrachloride adduct in excellent yield, in accord with the stability of the similar dipyridine compounds of silicon [5] and stannic tetrachlorides.[6] The absence of reaction between diethylaniline and germanium tetrachloride [2] was presumably due to the considerable greater steric hindrance in diethylaniline than in pyridine. The dipyridine–germanium tetrachloride adduct is white, crystalline, and insoluble in ether and pentane, but soluble in benzene and chloroform. It is rapidly hydrolysed in air.

With boiling alcohols in the presence of further pyridine it slowly gives pyridine hydrochloride and the germanium alkoxides (Table 1). Previous [7,8] methods for the formation of these alkoxides have involved very fast reactions; thus the slow reaction of the pyridine complex presents a possible method for the kinetic study of the alkoxide formation.

Ethanethiol and butane-1-thiol similarly produce the germanium sulphides in good yields (better than those of previous methods [9,10]). Tetrakisdiethylaminogermane was formed by the interaction of the complex with further pyridine and diethylamine.

Experimental.—Interaction of germanium tetrachloride and pyridine. The tetrachloride (13·06 g., 1 mol.) in pentane (50 c.c.) was added to pyridine (12·00 g., 2·5 mol.) in pentane (50 c.c.) at 0°. After 24 hr. the white precipitate was filtered off and washed with pentane (3 × 50 c.c.). Excess of solvent was removed at 0·2 mm., to leave the *dipyridine–germanium tetrachloride adduct* (22·36 g., 98%), m. p. 207—214° (decomp., sealed tube) [Found: C, 32·7;

[1] Johnson, *Chem. Rev.*, 1951, **48**, 259.
[2] Thomas and Southwood, *J.*, 1931, 2083.
[3] Trost, *Canad. J. Chem.*, 1952, **30**, 835.
[4] Johnson and Sidwell, *J. Amer. Chem. Soc.*, 1933, **55**, 1884.
[5] Harden, *J.*, 1887, **51**, 40.
[6] Pfeiffer, *Z. anorg. Chem.*, 1911, **71**, 97.
[7] Johnston and Fritz, *J. Amer. Chem. Soc.*, 1953, **75**, 718.
[8] Bradley, Kay, and Wardlaw, *Chem. and Ind.*, 1953, **746**.
[9] Backer and Stienstra, *Rec. Trav. chim.*, 1933, **52**, 1033.
[10] *Idem, ibid.*, 1935, **54**, 607.

H, 3·1; N, 7·4; Cl, 38·8%; *M*, 379 (ebullioscopic in benzene). $C_{10}H_{10}Cl_4GeN_2$ requires C, 32·2; H, 2·7; N, 7·5; Cl, 38·1%; *M*, 373].

Formation of germanium alkoxides. The complex (1 mol.), pyridine (2 mol.), and the alcohol (4 mol.) in benzene (75 c.c.) were refluxed for 100 hr. (reaction times less than 75 hr. gave much reduced yields). Volatile matter was removed at 20°/0·2 mm., and the residue was shaken with ether (50 c.c.) in order to precipitate pyridine hydrochloride. This was filtered off; removal of solvent at 20°/0·5 mm. left the crude alkoxide, which was distilled to give the pure product (Table 1). Each of these reactions was carried out on approx. 0·05 molar scale.

TABLE 1. *Germanium tetra-alkoxides.*

Alkyl	Yield (%)	B. p./mm.	n_D^{20}	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
Ethyl	73	75°/10	1·4061	37·6	7·7	38·0	7·9
n-Propyl	79	111°/10	1·4168	46·9	8·7	46·6	9·1
n-Butyl	91	88°/0·2	1·4271	52·1	9·7	52·6	9·9

Formation of the alkylthiogermanes. The complex (1 mol.), pyridine (2 mol.), and the thiol (4 mol.) in light petroleum (50 c.c.) (b. p. 60—80°) were heated at 150° for 25 hr. After cooling, pyridine hydrochloride and then solvent (at 20°/5 mm.) were removed. Distillation produced the pure products (Table 2). These reactions were carried out on approx. 0·05 molar scale.

TABLE 2. *Tetra-alkylthiogermanes.*

Alkyl	Yield (%)	B. p./mm.	n_D^{20}	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
Ethyl	73	151°/0·1	1·5886	30·9	6·0	30·3	6·3
n-Butyl	76	198°/0·5	1·5450	44·5	8·1	44·8	8·4

Formation of tetrakisdiethylaminogermane. The complex (3·94 g., 1 mol.), pyridine (1·67 g., 2 mol.), and diethylamine (3·08 g., 4 mol.) in pentane (50 c.c.) were heated at 120° for 30 hr. After cooling and filtration, removal of the solvent at 20°/0·5 mm. and distillation produced tetrakisdiethylaminogermane (2·63 g., 69%), b. p. 72°/0·7 mm., n_D^{20} 1·4726 (Found: C, 53·8; H, 10·8; N, 15·3. Calc. for $C_{16}H_{40}GeN_4$: C, 53·3; H, 11·1; N, 15·5%).

The author thanks Professor Geoffrey Wilkinson for encouragement and helpful discussions, and the Ethyl Corporation for a fellowship.

INORGANIC CHEMISTRY RESEARCH LABORATORIES,
IMPERIAL COLLEGE, LONDON, S.W.7.

[*Received, May 23rd.* 1958.]

763. *Per-rhenyl Fluoride.*

By E. E. AYNSLEY and M. L. HAIR.

PER-RHENYL FLUORIDE, ReO_3F, first obtained pure by Engelbrecht and Grosse,[1] is obtained in good yield together with iodine oxytrifluoride, IOF_3, and iodyl fluoride, IO_2F, by the reaction of potassium per-rhenate with iodine pentafluoride:

$$KReO_4 + IF_5 = ReO_3F + IOF_3 + KF$$
$$2IOF_3 = IO_2F + IF_5$$

Moreover, we have redetermined the m. p. and b. p. of rhenium oxypentafluoride, $ReOF_5$, and rhenium dioxytrifluoride, ReO_2F_3 (prepared from rhenium dioxide and elementary fluorine [2]), and a comparison of the three oxyfluorides of septavalent rhenium is given in the Table.

Oxyfluorides of septavalent rhenium.

	M. p.	B. p.	Colour
$ReOF_5$	35°	55°	Cream
ReO_2F_3	95	126	Pale yellow
ReO_3F	147	164	Yellow [1]

[1] Engelbrecht and Grosse, *J. Amer. Chem. Soc.*, 1954, **76**, 2042.
[2] Aynsley, Peacock, and Robinson, *J.*, 1950, 1622.

Experimental.—Preparation of per-rhenyl fluoride. Iodine pentafluoride (9 g.), prepared by burning dry iodine in a fluorine–nitrogen stream (40 : 60, v/v) and freed from dissolved fluorine and iodine heptafluoride by vacuum fractionation, was condensed on powdered potassium per-rhenate (2 g.). Only slight reaction occurred at room temperature, the solution becoming pale yellow. However, on heating the mixture under such conditions that the iodine pentafluoride was allowed to reflux in the reaction bulb (97°), the potassium per-rhenate dissolved completely to form a deep yellow solution from which a yellow sludge separated on cooling. Removal of excess of iodine pentafluoride under vacuum left a yellow residue which, when heated to 140° in a paraffin bath, yielded, first, further iodine pentafluoride, and then a yellow solid which formed as a glass in a trap cooled to 0° (Found: Re, 73·2; F, 7·9. Calc. for ReO_3F: Re, 73·6; F, 7·5%). The product had m. p. 147°, b. p. 164°, in agreement with the values given by Engelbrecht and Grosse.[1]

In the preparation of permanganyl fluoride, MnO_3F, from the reaction between potassium permanganate and iodine pentafluoride, an explosion always occurs if the potassium permanganate is in excess; [3] in the preparation of per-rhenyl fluoride from potassium per-rhenate and iodine pentafluoride there is never any danger of an explosion.

Preparation of iodine oxytrifluoride and iodyl fluoride. The white solid remaining in the reaction vessel was a mixture of potassium fluoride and iodyl fluoride. The latter was dissolved in boiling iodine pentafluoride, then separated from undissolved potassium fluoride and recrystallised as iodine oxytrifluoride, IOF_3 (Found: I, 63·4; F, 28·8. Calc. for IOF_3: I, 63·6; F, 28·5%). Heating the iodine oxytrifluoride to 110° in a vacuum again caused evolution of iodine pentafluoride, and iodyl fluoride remained as a fine powder (Found: I, 71·6; F, 10·9. Calc. for IO_2F: I, 71·3; F, 10·7%).

One of us (M. L. H.) thanks the Salters' Company for a Scholarship.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1. [*Received, May 27th,* 1958.]

[3] Aynsley, *J.*, 1958, 2425.

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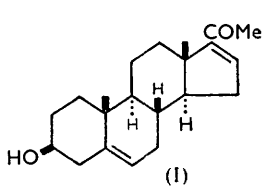
764. 16α-*Carboxyprogesterone.*

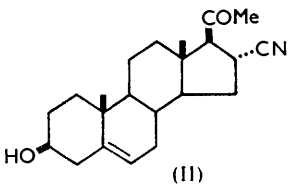
By B. ELLIS, V. PETROW, and (MISS) D. WEDLAKE.

PROLONGED treatment of 3β-hydroxypregna-5 : 16-dien-20-one (I) with potassium cyanide in boiling aqueous ethanol gave 16α-carboxy-3β-hydroxypregn-5-en-20-one, through the intermediate 16α-cyano-3β-hydroxypregn-5-en-20-one (II).

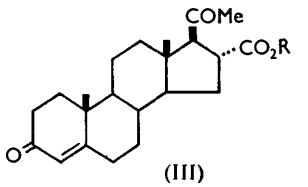
The cyano-group in the ketone (II) is assigned the α-configuration by application of the " rule of the rear." This configuration is retained by the carboxyl group formed on hydrolysis, since conversion of the 20-oxo-group of 16α-carboxy-3β-hydroxypregn-5-en-one



(I)



(II)



(III)

into a secondary alcohol group by reduction with sodium borohydride leads to acidic material devoid of γ-lactone properties. Molecular models indicate that γ-lactone formation is unlikely when an α-configuration of the 16-carboxyl group obtains and is unavoidable when this configuration is β.

16α-Carboxy-3β-hydroxypregn-5-en-20-one was converted into its methyl ester and thence by Oppenauer oxidation into the αβ-unsaturated ketone (III; R = Me). Saponification gave the required 16α-carboxyprogesterone (III; R = H).

Experimental.—Reaction of 3β-*hydroxypregna*-5 : 16-*dien*-20-*one with potassium cyanide.* The ketone (I) (15 g.), potassium cyanide (5 g.), ethanol (200 ml.), and water (50 ml.) were heated under reflux for 12 hr. After addition of ether (1 l.), the mixture was extracted with water (250 ml.) and the extract diluted with more water (200 ml.). Acidification to Congo-red gave a copious white precipitate which was collected, washed, and crystallised from aqueous ethanol, to give 16α-*carboxy*-3β-*hydroxypregn*-5-*en*-20-*one* (10 g.) in plates, m. p. 234—235°, $[\alpha]_D^{22}$ −113·5° (*c* 0·72) (Found: C, 73·1; H, 9·1%; equiv., 351. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%; equiv., 360).

In other experiments, in which the reaction period was reduced to 2—3 hr., the neutral fraction contained two nitrogenous compounds, one readily soluble and the other very sparingly soluble in ether. The former compound was purified from aqueous ethanol, to give 16α-*cyano*-3β-*hydroxypregn*-5-*en*-20-*one*, needles, m. p. 229—231°, $[\alpha]_D^{20}$ +3° (*c* 1·41) (Found: C, 77·1; H, 9·1; N, 4·3. $C_{22}H_{31}O_2N$ requires C, 77·4; H, 9·15; N, 4·1%). Prolonged hydrolysis of this with aqueous-ethanolic potassium hydroxide gave 16α-carboxy-3β-hydroxypregn-5-en-20-one, m. p. and mixed m. p. 234°. Treatment of the nitrile with acetic anhydride–pyridine at 100° gave the 3β-*acetate*, needles (from aqueous ethanol), m. p. 197—199°, $[\alpha]_D^{22}$ −2·5° (*c* 1·02) (Found: C, 75·3; H, 8·7. $C_{24}H_{33}O_3N$ requires C, 75·2; H, 8·65%).

The second sparingly-soluble reaction product, m. p. *ca.* 260°, proved difficult to purify. It was acetylated in pyridine at 100° to give (probably) 3β-*acetoxy*-16α-*carbamoylpregn*-5-*en*-20-*one*, needles (from acetone–hexane), m. p. 215—217° (Found: C, 71·3, 71·0; H, 8·7, 8·9. $C_{24}H_{35}O_4N$ requires C, 71·8; H, 8·6%).

Reduction of 16α-*carboxy*-3β-*hydroxypregn*-5-*en*-20-*one.* The carboxylic acid (3·6 g.) in methanol (100 ml.) was treated with sodium hydroxide (0·5 g.) in water (10 ml.), and then with sodium borohydride (1·5 g.). After 2½ hr. at room temperature, the mixture was acidified with acetic acid and carefully diluted until solid was no longer precipitated. The product was collected, washed, and dried at 100° to give material (3·4 g.) with m. p. 240—245°. This was very sparingly soluble in most organic solvents and could not be satisfactorily recrystallised. Titration with alkali gave equiv. 372 ($C_{22}H_{34}O_4$ requires equiv., 362). The infrared spectrum (for which we are indebted to Mr. M. T. Davies, B.Sc.), determined in Nujol suspension, revealed bands at 3411 and 3230 $cm.^{-1}$, corresponding to two differently situated hydroxyl groups. A broad band at 1686 $cm.^{-1}$ confirmed the presence of the carboxyl group.

3β*Hydroxy*-16α-*methoxycarbonylpregn*-5-*en*-20-*one*, prepared from the acid by treatment with hot methanolic hydrogen chloride, crystallised from methanol in needles, m. p. 208°, $[\alpha]_D^{23}$ −112·5° (*c* 1·03) (Found: C, 73·7; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·0%).

16α-*Methoxycarbonylprogesterone.* A solution of the foregoing ester (4 g.) in toluene (200 ml.) and *cyclo*hexanone (40 ml.) was distilled until 50 ml. of distillate had collected. After addition of aluminium *iso*propoxide (2·5 g.) in toluene (10 ml.), the mixture was refluxed for 2 hr., cooled, and washed with dilute sulphuric acid, then with water, and the solvents were removed by steam-distillation. The solid product was purified from aqueous methanol to give the *ester* as needles, m. p. 153—154°, $[\alpha]_D^{20}$ +12·5° (*c* 1·12) (Found: C, 74·0; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·15; H, 8·7%).

16α-*Carboxyprogesterone*, prepared from this ester by hot aqueous-methanolic potassium hydroxide, separated from aqueous methanol in plates, m. p. 250—255°, $[\alpha]_D^{20}$ +9·5° (*c* 1·2), $\lambda_{max.}$ 240 mμ (log ε 4·23) (Found: C, 72·9; H, 8·4; equiv., 360. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4; equiv., 358). [α] refer to chloroform solutions.

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CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1.

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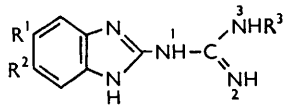
765. *The Synthesis of Some Benziminazoles.*

By R. M. Acheson, G. A. Taylor, and Muriel L. Tomlinson.

Several years ago a number of benziminazoles, structurally similar to " Paludrine," were synthesised [1] in the hope that they might have antimalarial properties or shed some light on the mode of action of " Paludrine " itself. Only one ($R^1 = R^2 = Cl$, $R^3 = Pr^i$ of the benziminazoles showed even slight antimalarial activity. Nevertheless, on screening as antibacterials the compounds containing chlorine showed considerable activity against a virulent human type of *M. tuberculosis* grown in Dubos medium containing " Tween 80 " (0·01%) and bovine albumin (0·2%). It was therefore of interest to synthesise other benziminazoles of the same type as potential chemotherapeuticals, and disappointing to find that none of the chloro-compounds ($R^1 = Cl$, $R^2 = H$, $R^3 = H$, Et, or Pr^i; $R^1 = R^2 = Cl$, $R^3 = H$, Me, Et, or Pr^i) showed appreciable activity against the H37Rv strain of *M. tuberculosis* in mice.



R^1	R^2	R^3	Activity *	R^1	R^2	R^3	Activity *
Me	H	Pr^i	4	Me	H	H	5
MeO	MeO	Pr^i	1	H	H	H	1
Cl	Cl	Pr^i	100	Cl	H	H	5
Me	Me	Pr^i	5	MeO	H	H	2
Cl	H	Pr^i	20				

* Max. dilution (10^{-4} ml./g.) for complete inhibition of growth.

From the screening *in vitro* it was clear that the chlorinated derivatives were the most promising as antituberculosis agents. Several more were therefore synthesised from the appropriate *o*-phenylenediamines and the dicyandiamides, and purified *via* the picrates in the usual way.[1] No difficulties were encountered except in attempts to combine *tert.*-butyldicyandiamide with 1 : 2-diamino-4 : 5-dichlorobenzene; here the original diamine was recovered as the picrate in over 70% yield and none of the desired product was obtained. The failure may be due to steric effects of the *tert.*-butyl group as *n*-butyldicyandiamide behaves normally in the condensation.[1]

1 : 2-Diamino-4 : 5-dichlorobenzene has been obtained [1] by a somewhat fickle catalytic hydrogenation of the corresponding dinitro-compound which is also not easy to prepare in quantity.[2] Reduction of the dinitro-compound with hydrazine hydrate in the presence of Raney nickel [3] gave poor yields of the diamine. An alternative synthesis was achieved through the hydrogenation of 1-amino-4 : 5-dichloro-2-nitrobenzene which had already been obtained by two methods.[4] In the shorter of these 2 : 4 : 5-trichloronitrobenzene was treated with ethanolic ammonia at 200°, and similar reactions with aliphatic amines have been described.[5] Re-investigation of the ammonia reaction showed that much charring took place at 200°, at 140—150° both the chlorine atoms activated by the nitro-group were replaced, yielding 1 : 5-diamino-4-chloro-2-nitrobenzene as the main product, while at 115° 1-amino-4 : 5-dichloro-2-nitrobenzene was obtained with minimum contamination.

Experimental.—*5-Chloro-2-(N³-ethylguanidino)benziminazole.* 4-Chloro-*o*-phenylenediamine dihydrochloride, obtained from 4-chloro-2-nitroaniline (34·6 g.) in the usual way,[1] was refluxed with ethyldicyandiamide (25·5 g.) in water (90 ml.) for 45 min. After treatment with charcoal the filtrate and washings were added to picric acid (42 g.) in boiling water (1·1 l.), the *benziminazole picrate* (80·4 g.), m. p. 225° (decomp.), being precipitated. It was collected, refluxed with just sufficient ethanol to form a paste, cooled, and collected again (59·7 g.; m. p. 235°). Further recrystallisation from ethanol–water (3 : 1 v/v) gave a yellow powder, m. p. 245°

[1] Acheson, King, and Spensley, *Nature*, 1947, **160**, 53; *J.*, 1948, 1366.
[2] Acheson and Taylor, *J.*, 1956, 4727.
[3] Brown and Nelson, *J. Amer. Chem. Soc.*, 1954, **76**, 5149.
[4] Beilstein and Kurbatow, *Annalen*, 1879, **196**, 221.
[5] Barlow and Ing., *J.*, 1950, 713.

(Found: C, 41·1; H, 3·1; Cl. 6·9. $C_{10}H_{12}N_5Cl,2C_6H_3O_7N_3$ requires C, 41·1; H, 3·2; Cl, 7·6%). The partially purified picrate (59·2 g.), mostly dissolved in hot ethylene glycol monomethyl ether (75 ml.), was treated with propan-1-ol (70 ml.) containing hydrogen chloride (13·9 g.). After a few moments precipitation of the *benziminazole dihydrochloride* was assisted by the addition of dry ether (1 l.). The hydrochloride [36·2 g.; m. p. 190—195° (decomp.)] was well washed with dry ether to remove picric acid and was purified by dissolution in propan-1-ol, treatment with charcoal, and precipitation by propanol containing hydrogen chloride (20%). The colourless crystalline product had m. p. 192—194° (decomp.) (Found: C, 37·1; H, 5·0; Cl, 32·1. $C_{10}H_{12}N_5Cl,2HCl,H_2O$ requires C, 36·6; H, 4·9; Cl, 32·4%).

5 : 6-*Dichloro*-2-(N^3-*methylguanidino*)*benziminazole*. 1 : 2-Diamino-4 : 5-dichlorobenzene (30 g.), methyldicyandiamide (20 g.), concentrated hydrochloric acid (60 ml.), and water (120 ml.) were refluxed for 1 hr. and poured into excess of 2N-sodium hydroxide. The yellow precipitate was washed with water, dissolved in a mixture of concentrated hydrochloric acid (40 ml.), water (100 ml.), and ethanol (100 ml.), and filtered into a hot solution of picric acid (40 g.) in water–ethanol (300 ml. + 100 ml.). The precipitated picrate was extracted twice with 50% aqueous ethanol (100 ml., 80 ml.) and converted into the *dihydrochloride* in 2-ethoxyethanol–tetrahydrofuran (4 : 1). It separated from aqueous methanol containing hydrogen chloride in fine needles, m. p. 263—265° (decomp.) (Found: C, 32·9; H, 3·5; N, 21·3. $C_9H_9N_5Cl_2,2HCl$ requires C, 32·6; H, 3·3; N, 21·2%). The *base*, precipitated from the aqueous dihydrochloride by ammonia, had m. p. 244° (Found: C, 42·3; H, 3·6; N, 27·3. $C_9H_9N_5Cl_2$ requires C, 41·9; H, 3·5; N, 27·1%).

5 : 6-*Dichloro*-2-(N^3-*ethylguanidino*)*benziminazole*. This was prepared similarly by using ethyldicyandiamide; the *hydrochloride* separated from water in pale brown needles, m. p. 259—260° (Found: C, 38·5; H, 4·2; N, 22·6. $C_{10}H_{11}N_5Cl_2,HCl$ requires C, 38·9; H, 3·9; N, 22·7%).

5 : 6-*Dichloro*-2-(N^3-iso*propylguanidino*)*benziminazole*. This was obtained as the *hydrochloride hemihydrate* from methanolic hydrochloric acid and had m. p. 206—211° (decomp.) (Found: C, 39·5; H, 4·6; N, 21·1. $C_{11}H_{13}N_5Cl_2,HCl,\frac{1}{2}H_2O$ requires C, 39·8; H, 4·5; N, 21·1%).

tert.-*Butyldicyandiamide*. *tert.*-Butylamine hydrochloride (111 g.) and sodium dicyandiamide (90 g.) were refluxed in butan-1-ol (600 ml.) for 24 hr. Filtration followed by evaporation *in vacuo* gave the *dicyandiamide* (130 g.) which separated from aqueous ethanol as colourless waxy crystals, m. p. 188—189° (decomp.) (Found: C, 51·4; H, 8·6. $C_6H_{12}N_4$ requires C, 51·4; H, 8·6%).

Methyldicyandiamide [6] was basic enough to form a *hydrochloride*, m. p. 161—163° (decomp.), which crystallised from water (Found: C, 21·4; H, 6·8; N, 33·2. $C_3H_6N_4,HCl,2H_2O$ requires C, 21·1; H, 6·5; N, 32·9%). Ethyldicyandiamide [1,6] formed a *picrate* which separated from water as a yellow powder, m. p. 204—205° (decomp.) (Found: C, 33·6; H, 3·7; N, 27·3. $C_4H_8N_4,C_6H_3O_7N_3,H_2O$ requires C, 33·4; H, 3·6; N, 27·3%).

1 : 2 : 4-*Trichloro*-5-*nitrobenzene*.[7] Nitric acid (110 ml.; *d* 1·42) was added dropwise (30 min.) to a stirred mixture of 1 : 2 : 4-trichlorobenzene (159 ml.) and concentrated sulphuric acid (455 ml.) originally at 40°, the temperature being kept below 70°. After an additional 30 min. at 60° the hot mixture was poured into water (3 l.). The precipitate was washed with water and on recrystallisation from ethanol (200 ml.) gave the nitro-compound (304 g., 84%) as pale yellow needles, m. p. 58·5°.

1-*Amino*-4 : 5-*dichloro*-2-*nitrobenzene*. (i) 1 : 2 : 4-Trichloro-5-nitrobenzene (150 g.), ethanol (250 ml.), and aqueous ammonia (500 ml.; *d* 0·880) were heated in a rotating autoclave at 115° ± 3° for 4½ hr. The solid product (113 g.) was collected, dried, and recrystallised from water (300 ml.)–acetone (600 ml.), the nitroamine forming orange needles (62 g.), m. p. 173—174°, raised to 175·5° on recrystallisation from acetic acid. The acetyl derivative, prepared by boiling acetic anhydride, separated from acetic acid in yellow needles, m. p. 123·5°.

Attempts to decrease the losses during purification of the crude material were unsuccessful. The solubilities of the monoamine and the contaminating diamine do not differ greatly, and mixed crystals are produced from most solvents.

When the ammonolysis was carried out at 140—153° the product (largely 1 : 5-diamino-4-chloro-2-nitrobenzene), after precipitation with water, had m. p. 178° depressed to 156—160°

[6] Hendry, Kenny, Murray, and Rose, *J.*, 1948, 1630.

[7] Holleman and van Haeften, *Rec. Trav. chim.*, 1921, **40**, 67, mention this preparation without giving details.

on mixture with 1-amino-4 : 5-dichloro-2-nitrobenzene. Refluxing with acetic anhydride containing a trace of sulphuric acid gave probably 1 : 5-diacetamido-4-chloro-2-nitrobenzene, which crystallised from acetic acid as a yellow powder, m. p. 238·5° (Found: C, 44·0; H, 3·7; N, 15·4. Calc. for $C_{10}H_{10}O_4N_3Cl$: C, 44·2; H, 3·7; N, 15·5%). " About 222° " is the m. p. given [8] for the chlorination product of 1 : 3-diacetamido-4-nitrobenzene.

(ii) 1 : 2-Dichloro-4 : 5-dinitrobenzene (0·5 g.) was heated and stirred rapidly with urea (1·0 g.) on an oil-bath. At *ca.* 160° two layers were formed, much gas was evolved, and after a few minutes the deep red mixture became homogeneous. The solid obtained on cooling crystallised from methanol; the least soluble fraction, the amine, separated in yellow needles, m. p. 178° (Found: C, 34·9; H, 1·9; N, 13·1. Calc. for $C_6H_4O_2N_2Cl_2$: C, 34·8; H, 1·9; N, 13·5%) (lit.,[9] m. p. 176°).

1 : 2-*Diamino*-4 : 5-*dichlorobenzene*. (i) 1-Amino-4 : 5-dichloro-2-nitrobenzene (20 g.) was hydrogenated (5 atm.) over Raney nickel in tetrahydrofuran (80 ml.) at room temperature. After filtration the solution was diluted with water, the diamine (16 g.) being precipitated. After recrystallisation from light petroleum (b. p. 100—120°) it had m. p. 161°. (ii) A solution of 100% hydrazine hydrate (20 ml.) in methanol (20 ml.) was added to one of 1 : 2-dichloro-4 : 5-dinitrobenzene (1·0 g.) in methanol (20 ml.) to which Raney nickel had been added. Then the mixture was heated on a water-bath for 10 min., by which time the solution was grey. The mixture was concentrated to a small volume and water (50 ml.) was added. The precipitate was collected and extracted with hot benzene, and the extract evaporated to dryness. The residue on recrystallisation from benzene and light petroleum gave grey crystals of the diamine (0·33 g., 45%), m. p. 161°. The *picrate* separated from aqueous ethanol in yellow needles, m. p. 182—184° (decomp.) (Found: C, 35·6; H, 2·1. $C_6H_6N_2Cl_2,C_6H_3O_7N_3$ requires C, 35·5; H, 2·2%). The *dibenzenesulphonyl derivative*, prepared in the usual way in pyridine, separated from acetic acid in colourless needles, m. p. 196—197° (Found: C, 47·6; H, 3·0. $C_{18}H_{14}O_4N_2Cl_2S_2$ requires C, 47·3; H, 3·1%) (lit.,[10] m. p. 186°). The diamine (0·14 g.) also reacted with pyrene-1 : 2-quinone (0·17 g.) in hot acetic acid, yielding 6 : 7-*dichloropyreno*(4′ : 5′-2 : 3)*quinoxaline* which was precipitated by water. It separated from acetic acid (600 ml.) in yellow needles (0·18 g.), m. p. 297° (Found: C, 70·6; H, 2·9. $C_{22}H_{10}N_2Cl_2$ requires C, 70·8; H, 2·7%).

We thank Dr. E. Schlittler, of Ciba Pharmaceuticals Inc., for arranging the *in vivo* tests, Dr. C. N. Iland for the *in vitro* data, and Mr. A. O. Plunkett for some technical assistance.

THE DYSON PERRINS LABORATORY, and THE DEPARTMENT OF BIOCHEMISTRY,
OXFORD UNIVERSITY. [*Received, June 4th*, 1958.]

[8] Morgan and Wootton, *J.*, 1905, **87**, 935.
[9] Blanksma, *Rec. Trav. chim.*, 1902, **21**, 420.
[10] Adams and Winnick, *J. Amer. Chem. Soc.*, 1951, **73**, 5687.

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766. *The Melting Points of* cis- *and* trans-cyclo*Hexane*-1 : 2-*diol Di*-p-*nitrobenzoates*.

By T. H. ELLIOTT.

THE recorded [1] melting points are 128—128·5° and 149—150°, respectively, but these should be transposed.

*cis-cyclo*Hexane-1 : 2-diol [2] gave a di-*p*-nitrobenzoate, m. p. 149° (Found: C, 58·1; H, 4·4; N, 6·5. Calc. for $C_{20}H_{18}O_8N_2$: C, 58·0; H, 4·4; N, 6·8%), and a 3 : 5-dinitrobenzoate, m. p. 169° (lit.,[1] 169°).

The *trans*-diol [3] gave a di-*p*-nitrobenzoate, m. p. 129—129·5° (Found: C, 58·4; H, 4·5; N, 6·5%), and a 3 : 5-dinitrobenzoate, m. p. 179° (lit.,[1] 179°).

Each ester was hydrolysed by alkali to the parent diol.

DEPT. OF PHARMACEUTICS, UNIVERSITY OF MALAYA. [*Received, May 9th*, 1958.]

[1] Wilson and Read, *J.*, 1935, 1269.
[2] Vogel, " A Textbook of Practical Organic Chemistry," 2nd Edn., 1954, p. 895.
[3] Roebuck and Adkins, *Org. Synth.*, Coll. Vol. III, 1955, p. 217.