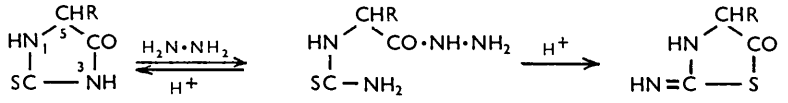
1016. *Thiohydantoins. Part III.* Reactions with Amino-compounds.*

By J. T. Edward and S. Nielsen.

As model studies for a modification of Schlack and Kumpf's procedure,[1,2] we have investigated the deacylation of 1-acyl-2-thiohydantoins by aqueous hydrazine. 1-Benzoyl-2-thiohydantoin and 1-acetyl-5-methyl-2-thiohydantoin readily afforded benzhydrazide and acethydrazide respectively; however, instead of the expected 2-thiohydantoins (I; R = H and Me) the products proved to be the α-thioureido-hydrazides (II; R = H and Me).[3] The action of acid on the hydrazide (II; R = Me) afforded the thiohydantoin (I; R = Me) again, and a third compound which was probably 2-imino-4-methyl-5-thiazolinone (III; R = Me).[4]



(I) (II) (III)

The high yields of these hydrazides (II; R = H and Me) were probably a consequence of low solubility in water. The reaction of aqueous hydrazine with 2-thiohydantoin and with 5-methyl-, 3-phenyl-, 5-phenyl-, 5-benzyl-, and 5-*iso*propyl-2-thiohydantoin was shown by paper chromatography to be still incomplete after one week, and crystalline hydrazides could not be isolated from the last four reactions. On the other hand, reaction of 5-methyl-2-thiohydantoin with excess of benzylamine or phenylhydrazine was complete in 24 hours, but the products could not be obtained crystalline.

Experimental.—Thioureidoacethydrazide (II; R = H). A solution of 1-benzoyl-2-thiohydantoin (0·5 g.) in 50% aqueous hydrazine (5 ml.) began to deposit colourless prisms of *thioureidoacethydrazide* after 2 min.; after 30 min. the hydrazide (0·32 g.), m. p. 190° (decomp.) (Found: C, 24·0; H, 5·2. $C_3H_8ON_4S$ requires C, 24·3; H, 5·4%), was collected. It was soluble in concentrated mineral acids and alkalis, but had negligible solubility in common organic solvents except hot glacial acetic acid.

The filtrate from the hydrazide, overnight at 0°, deposited benzhydrazide, obtained after recrystallisation from methanol as plates, m. p. and mixed m. p. 112°. By ascending chromatography on Whatman No. 1 paper, with butanol saturated with water as the solvent system (solvent A), it had R_F 0·68; with propanol–water 7 : 3 (v/v) (solvent B), R_F = 0·86. Identical R_F values were shown by an authentic specimen. The zones of benzhydrazide were located by sprays of the Folin–Denis reagent [2,5] (blue spot) or of an acidic solution of *p*-dimethylaminobenzaldehyde (yellow spot).

α-Thioureidopropionhydrazide (II; R = Me). The hydrazide began to be deposited within 20 min. of mixing from a solution of 1-acetyl-5-methyl-2-thiohydantoin (2·0 g.) in 50% aqueous hydrazine (10 ml.). After 12 hr. the *hydrazide* (1·9 g.) was collected: it had m. p. 182° (Found: C, 29·2; H, 6·2; S, 19·7. $C_4H_{10}ON_4S$ requires C, 29·6; H, 6·2; S, 19·7%). The filtrate on evaporation afforded acethydrazide, identified by m. p., mixed m. p., and chromatographic comparison with an authentic specimen (R_F 0·29 in solvent A, 0·53 in solvent B).

α-Thioureidopropionhydrazide was also formed by the action of hydrazine on 5-methyl-2-thiohydantoin. Its solubility behaviour was similar to that of thioureidoacethydrazide. With benzaldehyde in aqueous acid it gave pale yellow plates of *benzaldehyde α-thioureidopropionylhydrazone*, m. p. 201 (Found: C, 51·8; H, 5·5. $C_{11}H_{14}ON_4S$ requires C, 51·8; H, 5·6%).

* Part II, preceding paper.

[1] Schlack and Kumpf, *Z. physiol. Chem.*, 1926, **154**, 125; Waley and Watson, *J.*, 1951, 2394.
[2] Edward and Nielsen, *Chem. and Ind.*, 1953, 197.
[3] Cf. Fosse, Hagene, and Du Bois, *Compt. rend.*, 1924, **178**, 578.
[4] Edman, *Acta Chem. Scand.*, 1956, **10**, 761.
[5] Folin and Denis, *J. Biol. Chem.*, 1912, **12**, 239; 1913, **14**, 95.

The hydrazide (10 mg.) was dissolved in 5N-hydrochloric acid (2 ml.). After 2 hr., paper chromatography of the solution with solvent A and the Folin–Denis spray showed the presence of 5-methyl-2-thiohydantoin (R_F 0·69), and of traces of the hydrazide (R_F 0·21) and of a third compound (III?) (R_F 0·50).

Chromatographic examination of the reaction between hydrazine and 2-thiohydantoins. Solutions of 2-thiohydantoin and of 3-phenyl-, 5-phenyl-, 5-methyl-, 5-*iso*propyl-, and 5-benzyl-2-thiohydantoin (0·2 g.) in 50% aqueous hydrazine (2 ml.), after storage for one week, were evaporated to dryness. The residues were taken up in water and examined by ascending chromatography with solvent A. In all cases the Folin–Denis spray showed two zones, the first due to the original 2-thiohydantoin; the second zone also reacted with *p*-dimethylaminobenzaldehyde, and so was a thioureidohydrazide (II). R_F values were as follows:

Substituent	—	3-Ph	5-Ph	5-Me	5-Pr^i	5-CH_2Ph
2-Thiohydantoin	0·45	0·75	0·75	0·69	0·90	0·90
Thioureidohydrazide	0·10	0·19	0·19	0·22	0·40	0·45

Reaction of 5-methyl-2-thiohydantoin with benzylamine and phenylhydrazine. The thiohydantoin (0·5 g.) was dissolved in benzylamine (3 ml.) and in phenylhydrazine (3 ml.). After 24 hr. the excess of base was removed at reduced pressure. The residual syrups could not be crystallised; paper chromatographic examination with solvent A showed a compound, R_F 0·82, from benzylamine and another compound, R_F 0·75, from phenylhydrazine, and the absence of 5-methyl-2-thiohydantoin in both cases.

We are grateful to Professor M. Stacey, F.R.S., for interest and encouragement, to the University of Birmingham for an I.C.I. Research Fellowship (to J. T. E.) and to the Department of Scientific and Industrial Research for a grant (to S. N.).

Department of Chemistry, The University,
Edgbaston, Birmingham, 15.

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1017. *Analogues of Aminacrine and Rivanol Derived from 1 : 10-Diaza-anthracene.*

By D. M. Besly and A. A. Goldberg.

5-Aminoacridine (aminacrine) and 5 : 8-diamino-3-ethoxyacridine (rivanol) are valuable antibacterial agents for application to wounds. It was of interest to prepare analogues containing the 1 : 10-diaza-anthracene nucleus in order to determine whether the extra ring-nitrogen atom increased solubility and antibacterial activity.

2-Chloro-4-nitrobenzoic acid with 5-amino-2-methoxypyridine gave 2-(2-methoxy-5-pyridylamino)-4-nitrobenzoic acid. Cyclisation by the Magidson–Grigorovski method yielded 9-chloro-2-methoxy-6-nitro-1 : 10-diaza-anthracene which was converted by ammonia in phenol into the 9-amino-6-nitro-compound. Reduction with iron then gave the required 6 : 9-diamine.

9-Amino-2-methoxy-1 : 10-diaza-anthracene was obtained from *o*-chlorobenzoic acid and 5-amino-2-methoxypyridine by the same route. Attempts to prepare 9-amino-1 : 10-diaza-anthracene were not successful because of the failure of the unsubstituted 2-3′-pyridylaminobenzoic acids [1] to undergo cyclisation.

Experimental.—*2-(2-Methoxy-5-pyridylamino)benzoic acid.* A mixture of *o*-chlorobenzoic acid (15·6 g., 0·1 mol.), anhydrous potassium carbonate (14 g., 0·1 mol.), 5-amino-2-methoxypyridine (9 g., 0·075 mol.), and a trace of copper bronze–cuprous iodide catalyst was stirred at the b. p. with pentyl alcohol (100 c.c.) for 3 hr.; water was separated by a Dean and Stark apparatus. The alcohol was removed in a current of steam, the residual solution filtered (charcoal) and adjusted with 5N-hydrochloric acid to pH 4, and the precipitate collected. Crystallisation from boiling aqueous ethanol gave the *acid* (8 g., 48%) in grey needles, m. p. 162—165° [Found: *M* (by titration), 242; N, 11·6%. $C_{13}H_{12}O_3N_2$ requires *M*, 244; N, 11·5%].

[1] Besly and Goldberg, *J.*, 1954, 2448.

9-*Chloro*-2-*methoxy*-1 : 10-*diazanthracene*. The foregoing acid (12 g.) was refluxed with phosphoryl chloride (72 c.c.) for 6 hr., the excess of reagent distilled off, and the residual oil poured on crushed ice (900 g.) and aqueous ammonia (300 c.c.; *d* 0·88). After being kept overnight at 0° the greenish-yellow precipitate was collected (12 g.; m. p. 130°), washed with water, and dried at 15°/10 mm. (KOH). The *chloro*-compound crystallised from ligroin (b. p. 80—100°) in pale yellow needles, m. p. 140° (Found: N, 11·3; Cl, 15·7. $C_{13}H_9ON_2Cl$ requires N, 11·5; Cl, 14·6%).

9-*Amino*-2-*methoxy*-1 : 10-*diaza-anthracene hydrochloride*. The foregoing compound (5·5 g.) was heated with dry phenol (30 g.) for 1 hr. at 110° and then ammonium carbonate (10 g.) added as rapidly (*ca.* ½ hr.) as frothing would permit. After a further hour at 110°, the cooled mixture was poured into anhydrous ether (250 c.c.). The yellow precipitate (4·5 g.; m. p. 270°), on crystallisation from 0·1N-hydrochloric acid (9 c.c./1 g.) and then dilute aqueous ammonium chloride, gave the pure *hydrochloride* in pale yellow needles, m. p. 288° (Found: equiv., 261; N, 16·3; Cl, 15·4%. $C_{13}H_{12}ON_3Cl$ requires equiv., 261·5; N, 16·1; Cl, 13·6%).

2-(2-*Methoxy*-5-*pyridylamino*)-4-*nitrobenzoic acid*. 2-Chloro-4-nitrobenzoic acid (54 g.), potassium carbonate (38 g.), copper bronze (0·5 g.), cupric oxide (0·5 g.), and 5-amino-2-methoxypyridine (27 g.) were stirred with pentyl alcohol (300 c.c.) at the b. p. for 6 hr. Treatment as described above then gave the *acid* (49 g., 78%) as an orange powder which crystallised from acetic acid (50 c.c./g.), as orange needles, m. p. 250° [Found: *M* (by titration), 284; N, 14·7%. $C_{13}H_{11}O_5N_3$ requires *M*, 289; N, 14·5%].

9-*Chloro*-2-*methoxy*-6-*nitro*-1 : 10-*diaza-anthracene*. The foregoing acid (10 g.) was cyclised by refluxing with phosphoryl chloride (80 c.c.) for 6 hr. and the mixture treated as above. The product (9·5 g.) had m. p. 210—214°; the pure *compound* separated from carbon tetrachloride in pale yellow needles, m. p. 218—220° (Found: N, 14·5; Cl, 12·4. $C_{13}H_8O_3N_3Cl$ requires N, 14·5; Cl, 12·2%).

9-*Amino*-2-*methoxy*-6-*nitro*-1 : 10-*diaza-anthracene*. The foregoing compound (21 g.) was heated with dried phenol (150 g.) at 110° for 1 hr. and then powdered ammonium carbonate (50 g.) was added with occasional stirring during 1 hr. After a further hour at 110° the mixture was poured into excess of anhydrous ether, and the crude product (13·6 g.; m. p. 285°) collected. The pure *hydrochloride monohydrate* separated from dioxan–water–acetone in orange needles, m. p. 300° (Found: N, 17·3; Cl, 10·8. $C_{13}H_{11}O_3N_4Cl,H_2O$ requires N, 17·2; Cl, 10·9%).

6 : 9-*Diamino*-2-*methoxy*-1 : 10-*diaza-anthracene hydrochloride*. A solution of stannous chloride dihydrate (30 g.) in 10N-hydrochloric acid (30 c.c.) was added portionwise to a suspension of the foregoing nitro-compound (5 g.) in acetic acid (60 c.c.) stirred at 50°. The nitro-compound dissolved with evolution of heat and a crystalline precipitate was rapidly formed. After ½ hour's stirring the mixture was chilled, then filtered on sintered glass, and the solid stirred with ice and 5N-sodium hydroxide. The diamine was collected and dissolved in methanol (100 c.c.) containing a slight excess of hydrochloric acid, and hydrogen sulphide passed in. The filtered (charcoal) solution was diluted with boiling water to incipient precipitation and chilled: the *hydrochloride* separated as an orange powder, m. p. 296° (Found: N, 19·8; Cl, 13·0. $C_{13}H_{13}ON_4Cl$ requires N, 20·2; Cl, 12·8%).

Antibacterial activitites. The bacteriostatic activities against a series of Gram-negative and Gram-positive organisms are shown in the Table as the dilution potential (pD) which completely inhibits growth of the organism (inoculum 2 × 10^6 organisms/10 c.c. of medium) in Lab-Lemco broth incubated at 37° for 48 hr. (pD *x* means a dilution of 1 part compound in 10^x parts broth.

Organism	Compound * I	II	III	IV
Staphytococcus pyogenes aureus	5·1	4·6	4·9	4·8
Streptococcus haemolyticus (Aronson)	5·1	5·2	5·5	5·7
Bacillus coli	4·8	4·9	4·6	5·5
Bacillus proteus	4·8	4·0	4·0	3·0
Pseudomonas pyocyaneous	3·3	3·3	4·6	3·0
Bacillus subtilis	5·1	4·9	5·2	4·8

* I, 5-Aminoacridine hydrochloride (aminacrine); II, 9-amino-2-methoxy-1 : 10-diaza-anthracene hydrochloride; III, 5 : 8-diamino-3-ethoxyacridine hydrochloride (rivanol); IV, 6 : 9-diamino-2-methoxy-1 : 10-diaza-anthracene hydrochloride.

RESEARCH DEPT., WARD, BLENKINSOP & CO., LTD.,
ANGLO ESTATE, SHEPTON MALLET, SOMERSET.

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1018. *Preparation of Carbonyl Compounds by Use of Dinitrogen Tetroxide. Part II.*[1] *Alkyl Aryl Ketones.*

By J. GRUNDY.

FIELD and GRUNDY[1] oxidised benzyl alcohols with dinitrogen tetroxide to prepare aromatic aldehydes; application of this reagent to the preparation of aryl alkyl ketones is now reported. In combination with the aldehyde preparation,[1] the method is useful for introducing an acyl in place of a carboxyl group: $R{\cdot}CO_2H \longrightarrow R{\cdot}CH_2{\cdot}OH \longrightarrow R{\cdot}CHO \longrightarrow R{\cdot}CHR'{\cdot}OH \longrightarrow R{\cdot}COR'$. The acyl group introduced is unambiguously oriented, and the method can be applied to, *e.g.*, *o*-halogenoaryl alkyl ketones.

Interaction of organocadmium compounds and acid chlorides[2] provides a valuable conversion of a carboxylic acid into a ketone; the use of dinitrogen tetroxide is, however, a still simpler technique and even in the four-stage process from the acid will give comparable yields.

The intermediate carbinols were usually obtained from the appropriate aromatic aldehyde and Grignard reagent, an excess of the latter preventing contamination of the carbinol with starting aldehyde. With methoxy-aldehydes some dealkylation occurred.

Reaction of the carbinols and dinitrogen tetroxide in chloroform followed the course previously described. Steric retardation of the reaction rate was observed with *o*-substituted 1-phenylethanols. Production of tars on distillation of reaction mixtures even at reduced pressures and liberation of dinitrogen tetroxide suggested formation of intermediates. However, residual intermediate was decomposed smoothly when the reaction mixture was heated on the water-bath or steam-distilled; the latter was the best method of isolating the ketones. The yields of ketones obtained are given in Table 1.

TABLE 1.

Ketone	Yield (%)	Ketone	Yield (%)	Ketone	Yield (%)
Acetophenone	98	*o*-Chloroacetophenone	95	*o*-Methoxyacetophenone	90
Propiophenone	98	*m*-Chloroacetophenone	90	*p*-Methoxyacetophenone	90
Butyrophenone	98	*p*-Chloroacetophenone	92	*m*-Methylacetophenone	94
Valerophenone	96	*o*-Bromoacetophenone	93	*p*-Methylacetophenone	95
Octyl phenyl ketone	92	*m*-Bromoacetophenone	91	*p*-Nitroacetophenone ...	88
		p-Bromoacetophenone	92	Benzophenone	89

Experimental.—Dinitrogen tetroxide. This was prepared as indicated previously[1] and the same concentration used.

Preparation of carbinols. The Grignard reagent was prepared in ether in the usual way from the alkyl iodide; the expected yields were based on the results of Gilman *et al.*[3] The aldehyde (0·6 mol.) in ether was added, and the cooled mixture decomposed by aqueous ammonium chloride. The carbinols were isolated in the usual way, yields being given in Table 2.

TABLE 2. *Yields of carbinols* $R{\cdot}C_6H_4{\cdot}CHR'{\cdot}OH$.

R	R′	B. p./mm.	Yield (%)	R	R′	B. p./mm.	Yield (%)	R	R′	B. p./mm.	Yield (%)
o-Cl	Me	80°/2	74	*m*-Br	Me	98°/2·5	78	*m*-Me	Me	100/4	76
m-Cl	Me	98/4·5	92	*p*-Br	Me	94/2	56	*p*-Me	Me	102/8	68
p-Cl	Me	90/2·5	70	*o*-MeO	Me	99/3·5	56	H	n-C_8H_{17}	130—134/2·5	60
o-Br	Me	100/3·5	85	*p*-MeO	Me	104/3	62				

1-p-*Nitrophenylethanol.* This was prepared as described by Ford-Moore and Rydon.[4]

Preparation of ketones. A solution of the carbinol (0·05—0·1 mole) in dry chloroform (3 vol.) was cooled in an ice-bath and a slight excess of the dinitrogen tetroxide solution added.

[1] *J.*, 1955, 1110, is considered to be Part I.
[2] Shirley, "Organic Reactions," Vol. 8, p. 28.
[3] Gilman, Zoellner, and Dickey, *J. Amer. Chem. Soc.*, 1929, **51**, 1579; Gilman and McCracken, *ibid.*, 1923, **45**, 2462.
[4] Ford-Moore and Rydon, *J.*, 1946, 679.

The mixture was kept in the bath for 1 hr., then at room temperature for about 6 hr. or overnight in the refrigerator. Finally it was washed with the calculated amount of sodium carbonate solution (10%) and then with water. Solvent was removed (water-bath), heating being continued until oxides of nitrogen were no longer evolved. Steam-distillation or distillation at reduced pressure then gave the ketone.

Identification of ketones. The ketones were characterised as the following 2 : 4-dinitrophenylhydrazones, prepared according to Brady's method [5] and recrystallised from xylene: acetophenone, m. p. and mixed m. p. 247—248°; propiophenone, m. p. 192—193° (Vogel [6] gives m. p. 191°); butyrophenone, m. p. 194—195° (Vogel [6] gives m. p. 190°); valerophenone, m. p. 165—166° (Vogel [6] gives m. p. 166°); n-*octyl phenyl ketone*, m. p. 238—239° (Found: N, 14·1. $C_{21}H_{26}O_4N_4$ requires N, 14·0%); benzophenone, m. p. 242—243 (lit.,[6,7] m. p. 238°, 240—241°); *o*-chloroacetophenone, m. p. 204—205° (lit.,[8] m. p. 206°); m-*chloroacetophenone*, m. p. 207—208° (Found: N, 16·6. $C_{14}H_{11}O_4N_4Cl$ requires N, 16·7%); *p*-chloroacetophenone, m. p. 240—241° (Vogel [6] gives m. p. 239°); *o*-bromoacetophenone, m. p. 186—187 (lit.,[9] m. p. 187°); m-*bromoacetophenone*, m. p. 225—226° (Found: N, 14·7. $C_{14}H_{11}O_4N_4Br$ requires N, 14·7%); *p*-bromoacetophenone, m. p. 232—233° (Vogel [6] gives m. p. 230°); *o*-methoxyacetophenone, m. p. 191—192° (lit.,[10,11] m. p. 185°, 196—198°); *p*-methoxyacetophenone, m. p. 225—226° (lit.,[6,11] 220°, 233—234°); *m*-methylacetophenone, m. p. 207—208° (Vogel [6] gives m. p. 207°); *p*-methylacetophenone, m. p. 256—257° (Vogel [6] gives m. p. 258°); and p-*nitroacetophenone*, m. p. 268—269° (Found: N, 20·1. $C_{14}H_{11}O_6N_5$ requires N, 20·3%).

BRUNEL COLLEGE OF TECHNOLOGY, ACTON, LONDON, W.3. [*Received, April 8th*, 1957.]

[5] Brady, *J.*, 1931, 757.
[6] Vogel, " Practical Organic Chemistry," Longmans Green, London, 1948.
[7] Roberts and Green, *J. Amer. Chem. Soc.*, 1946, **68**, 214.
[8] Borsche and Scriba, *Annalen*, 1939, **541**, 283.
[9] Borsche and Herbert, *ibid.*, 1941, **546**, 297.
[10] Pinder and Smith, *J.*, 1954, 113.
[11] Borsche and Barthenheier, *Annalen*, 1942, **553**, 250.

1019. *The Mechanism of the Vapour-phase Bromination of Naphthalene.*

By E. A. HALEVI, ISRAEL LOEFF, and GABRIEL STEIN.

IN Wibaut, Sixma, and Suyver's experiments [1] bromine and naphthalene were passed, in nitrogen, over glass wool or pumice at 250—600°. The percentage of β-bromonaphthalene in the monobromonaphthalene fraction rises from a low value at 250° along a sigmoid curve, which has maximum slope at 450—480°, and then approaches 50% asymptotically (curve through □ in the Figure). They concluded that bromination occurs *via* two competing mechanisms, each predominant in a different range: (i) at low temperatures, an electrophilic reaction at the packing surface favouring α-substitution, and (ii) at high temperatures, abstraction of hydrogen atoms by atomic bromine to form naphthyl radicals, which then react with molecular bromine. The first step was assumed to have a very low activation energy, and to be unselective with regard to production of α- and β-naphthyl radicals.

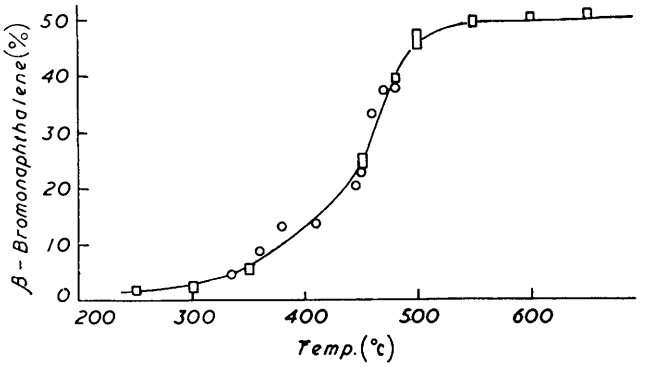
There appears to be no direct proof for these mechanisms. Korvezee and Scheffer [2] showed that any two competing reactions, both of first order with respect to bromine, could be made to yield a theoretical curve in equally good agreement with experiment. The large number of virtually freely adjustable parameters available seem to make even this restriction of kinetic order unnecessarily stringent. Moreover, the experiments involved packed vessels, so that there is no experimental evidence that the low-temperature

[1] (*a*) Suyver and Wibaut, *Rec. Trav. chim.*, 1945, **64**, 65; (*b*) Wibaut, Sixma, and Suyver, *ibid.*, 1949, **68**, 525; (*c*) Sixma, *ibid.*, p. 915; (*d*) Sixma and Wibaut, *ibid.*, 1950, **69**, 577.
[2] Korvezee and Scheffer, *ibid.*, p. 497.

reaction is heterogeneous. They concluded that it must be so from analogy with electrophilic liquid-phase bromination and the assumption that a heterolytic reaction in the vapour phase must involve either a three-body collision or, more plausibly, a surface reaction.

We have determined the product ratio under conditions different from those of ref. 1, using (*a*) a static system, (*b*) an unpacked vessel, and (*c*) no diluent gas.

(*a*) *Thermal Bromination.*—Approximately equimolar quantities of bromine and naphthalene (the latter in slight excess) were mixed in an evacuated vessel, preheated to the required temperature. After reaction the products were condensed, and the monobromonaphthalene fraction was distilled off *in vacuo*, the β/α ratio being determined in it spectrophotometrically (Figure, O).



Up to 480° our results duplicate Wibaut, Sixma, and Suyver's [1] quite well. Above 480° our results (not shown) became erratic, the percentage of β-bromonaphthalene being abnormally low, usually 20—30%.

(*b*) *Surface Effect.*—Although our method was unsuitable much above 480°, it appeared that surface effects could still be responsible for the erratic results there. Brominations were carried out in presence of Pyrex wool. Even at relatively low temperatures, increase of surface-to-volume ratio raised the yield of β-bromonaphthalene well above the value obtained in unpacked vessels, as follows: at 360°, 20·3%; at 370°, 22·4%. Therefore some surface reaction must occur, but the results are incompatible with the assumption [1] of a surface reaction's favouring α-bromination.

We tried to eliminate surface effects by " curing " the reaction vessels by coating them with carbon according to Maccoll and Thomas's method.[3] In " cured " vessels, our results agreed with those of ref. 1 at higher temperatures, within our large experimental error, so that by avoiding surface effects, and thus presumably obtaining homogeneous reactions, we could duplicate the findings of the previous workers over our entire working range.

Experiments were also done to determine whether α- and β-bromonaphthalene isomerise on glass in our conditions, as they do under the influence of ferric salts [1b] or silica gel,[4] by treating β-bromonaphthalene under various conditions. Isomerisation was much too slow to account for our erratic results in " uncured " vessels at high temperatures, at which bromination is virtually instantaneous. Moreover, synthetic mixtures of the approximate product composition did not equilibrate appreciably.

(*c*) *Photochemical Bromination.*—We confirmed that there are two competing mechanisms of bromination of naphthalene, but our duplication of the results of ref. 1 under such very different conditions showed that neither is heterogeneous. Wibaut, Sixma, and

[3] Maccoll and Thomas, *J.*, 1955, 980.
[4] Mayer and Schiffner, *Ber.*, 1934, **67**, 67.

Suyver's high-temperature mechanism, while still unproved, appears plausible. Their low-temperature mechanism, however, is untenable. Instead, direct attack of atomic bromine on carbon, with synchronous or subsequent elimination of a hydrogen atom, can be postulated. The higher free valence of the α-position [5] would lead to preferential substitution there. A crude calculation confirms that the equilibrium concentration of bromine atoms is probably high enough, even at lower temperatures, to account for the rate of bromination.

To determine whether the low-temperature brominations required atomic bromine, we did brominations under illumination. If both mechanisms were due to atomic bromine, the isomer ratio would not be altered. The experiments were qualitative, the unmodified reaction vessel being illuminated by two 500 w projection lamps. The results (% of β-isomer) are shown in the Table.

	300°	320°	350°	380°	400°	420°
Thermal (from Figure, curve)	2·5	3·4	5·5	8·5	11·2	15·0
Light	1·3	7·6	8·3, 7·9	13·9	26·1	27·2, 22·7

Above 350° the proportion of β-bromonaphthalene clearly increases. Thus increase of the standing concentration of bromine atoms photochemically accelerates the non-selective reaction preferentially, and does so at temperatures at which this mechanism is significant even under thermal conditions.

We conclude that two *homogeneous* mechanisms are involved, only the one favouring a high β/α ratio requiring bromine atoms. The high-temperature mechanism of ref. 1, the rate-determining step of which is

$$Br\cdot + C_{10}H_8 \longrightarrow HBr + C_{10}H_7\cdot \quad . \quad . \quad . \quad . \quad . \quad (1)$$

appears reasonable. However their assumption [1] that the activation energy of this step is 0—5 kcal./mole does not seem justified. As the dissociation energy of the C–H bond in naphthalene should be close to that in benzene (106 kcal./mole [6]), the dissociation energy of H–Br is approximately 86 kcal./mole, and as the reverse reaction of (1) should require [7] 0—2 kcal./mole, the activation energy of reaction (1) should be about 20 kcal./mole. The lack of selectivity of reaction by this mechanism would arise even if the rate-determining step were activated, provided the strengths of the C–H bonds in the α- and the β-position are the same.

A reasonable interpretation of the low-temperature mechanism involves the reaction of a bromine molecule with naphthalene. Bergmann [10] has suggested an addition–elimination sequence. One *a priori* objection is that these reactions are generally presumed to be heterolytic and therefore not characteristic homogeneous gas-phase reactions. However, Maccoll and Thomas's [8] pyrolyses of alkyl bromides, showing that homogeneous elimination of HBr can take place and partakes of considerable heterolytic character, disfavour this argument against the molecular elimination mechanism.

That illumination increases the percentage of β-isomer appreciably only at the higher temperatures suggests that the small but increasing percentage of β-isomer produced thermally at low temperatures arises from the " molecular " mechanism, as postulated by the previous workers,[1,2] who suggest a difference of 3—4 kcal./mole between reaction at the α- and the β-position.

Experimental.—Materials. α-Bromonaphthalene was prepared from α-naphthylamine by the Sandmeyer reaction and repeatedly fractionally distilled under reduced pressure. The β-isomer was similarly prepared by van der Kam's method,[9] twice steam-distilled from an

[5] Coulson, " Valence," Oxford Univ. Press, 1952, p. 255.
[6] Landolt–Börnstein, " Tabellen," Atom und Molekular Physik, Band I, 2 Teil, Molekeln I, 1951.
[7] Szwarc, *Chem. Rev.*, 1950, **47**, 81.
[8] Maccoll and Thomas, *Nature*, 1955, **176**, 392.
[9] van der Kam, *Rec. Trav. chim.*, 1926, **45**, 569.
[10] Bergmann, personal communication.

alkaline medium, and recrystallised (alcohol). Naphthalene was from B.D.H. (" for Molecular-weight Determination "). *n*-Hexane (Philips Petroleum Co., U.S.A.), stated to contain more than 99% of *n*-hexane, was redistilled several times.

Method. The reaction vessel was a Pyrex glass tube, 28 mm. in diameter and 30—35 cm. long (vol. *ca.* 200 c.c.). A side arm, connected to a vacuum system, contained a bromine ampoule with a magnetic breaker. Where a " cured " vessel was required, its interior surface was carbonised [3] by pyrolysis of alkyl bromide in the evacuated vessel at about 400°.

An ampoule containing naphthalene was sealed to the bottom of the vessel; 1·5—2 mmoles of naphthalene and bromine were used, the former being in slight excess. The whole vessel was evacuated to 10^{-3}—10^{-4} mm., sealed off, and put into the preheated oven, the naphthalene in the sealed-on ampoule being kept in liquid nitrogen. The bromine ampoule was broken and the naphthalene allowed to warm, so that the bromine and naphthalene distilled into the reaction vessel. The reaction was practically instantaneous at the higher temperatures and took 30—60 min. at the lowest temperatures. As the reaction reached completion, the products were condensed in the original naphthalene ampoule.

The photochemical experiments were performed in the same Pyrex apparatus. Unfiltered illumination from two 500 w projection lamps was employed so that only wavelengths above 3000 Å were effective.

Analysis. The products were transferred with diethyl ether to a small distillation flask and the ether was removed under reduced pressure. Excess of naphthalene was sublimed off at 80°/7 mm. on a cold finger containing solid carbon dioxide–ethanol. The monobromides were then distilled at about 130°/<7 mm. the b. p.s of the dibromides being considerably higher at this pressure. Ultraviolet absorption spectra of the two monobromides in *n*-hexane were measured with a Beckman Model D.U. spectrophotometer.

Because of the similarity of the absorption curves of the monobromonaphthalenes, we measured the optical densities of mixtures at 10 wavelengths between 2600 and 2950 Å, and reduced the results to two simultaneous equations by the method of least squares.

Spectrophotometric analysis were generally reliable to about ±2% of β-bromonaphthalene.

HEBREW UNIVERSITY, JERUSALEM. [*Received, May 16th,* 1957.]

1020. *Tetra-aquopalladium*(II) *Perchlorate.*

By STANLEY E. LIVINGSTONE.

PALLADIUM perchlorate, previously known only in aqueous perchloric acid solution,[1,2] has now been isolated as a crystalline tetrahydrate which deliquesces in moist air. The water of crystallisation is not removed *in vacuo* (P_2O_5) and so the solid probably contains the square planar ion $[Pd(H_2O)_4]^{2+}$, hitherto unknown in a simple salt.

The absorption spectrum in 1M-perchloric acid shows a maximum at 382 mμ (ε 200) a minimum at 310 mμ (ε 60). The aqueous solution of the compound darkens at first, but equilibrium is reached after some hours at room temperature; the conductance and absorption spectrum [$\lambda_{max.}$ 268 mμ (ε 4800)] remain unaltered after 7 days. The values of the molecular conductivity (Λ) in water at 25° are:

v (l.)	20	100	1000
Λ (mhos)	611	710	788

The pH of a 10^{-2}M-solution is 1·8, and at 10^{-3}M, 2·8. The addition of sodium perchlorate and subsequent boiling precipitates hydrated palladium(II) oxide. The brown aqueous solution is therefore a collodial suspension of hydrated palladium(II) oxide.

The hydrated palladium(II) ion is stable in solution only at low pH and in the absence of any ligand capable of co-ordinating to palladium. These conditions are fulfilled in

[1] Templeton, Watt, and Garner, *J. Amer. Chem. Soc.*, 1943, **65**, 1608.
[2] Sundaram and Sandell, *ibid.*, 1955, **77**, 855.

perchloric acid solutions at concentrations greater than 0·1M with respect to perchloric acid.

Experimental.—Tetra-aquopalladium(II) *perchlorate.* Palladium sponge was dissolved in concentrated nitric acid, perchloric acid (72%) added, and the solution heated till it fumed strongly; on cooling, it deposited brown needles of the *perchlorate.* These were washed with perchloric acid, pressed between filter papers, and dried *in vacuo* (over NaOH then P_2O_5) (Found: Cl, 18·9; Pd, 27·9. $H_8O_{12}Cl_2Pd$ requires Cl, 18·8; Pd, 28·2%).

Spectra. The absorption spectra were obtained on a Unicam S.P. 500 spectrophotometer, I cm. quartz cells being used.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.

[*Received, June 3rd,* 1957.]

1021. *Simple Preparation of* N^1*-Substituted* N^4N^4*-Phthaloyl-, -Succinoyl-, and -Adipoyl-sulphanilamides.*

By M. Z. BARAKAT, S. K. SHEHAB, and M. M. EL-SADR.

PREVIOUSLY it was reported that sulphapyridine with succinic and phthalic anhydrides at <100° gives acid amides $HO_2C{\cdot}X{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHY$ but at >100° gives the imides $X(CO)_2N{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHY$. With maleic anhydride the acid amide is the sole product, even at 190°. None of the diamides (I) is obtained in condensations with an-

(I) $X(CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHY)_2$

hydrides.[1,2] Other methods have been reported for the preparation of *p*-succinimidobenzenesulphonamide[3] and (*p*-phthalimidobenzenesulphonamido)pyridine.[4] We now report a general and simple method for preparing the imides: it consists of fusing succinic or phthalic acid with a sulphonamide at 200° for 30 minutes. It is analogous to the recent preparation of *N*-arylphthalimides.[5] Fusing adipic acid with sulphanilamide or certain derivatives yields the corresponding diamides (I).

We have thus prepared several known N^4N^4-succinimido- and -phthalimido-derivatives of sulphanilamides, as well as some new imides for chemotherapeutic testing.

Experimental.—The imides and diamides melted with decomposition, gave positive sodium fusion tests for nitrogen and sulphur, and negative diazotisation and acidity tests, and did not produce a colour with 10% alcoholic potassium hydroxide (cf. ref. 5).

Succinic acid (1·18 g., 0·01 mole) or phthalic acid (1·66 g., 0·01 mole) was heated with sulphanilamide (1·72 g., 0·01 mole), or an analogue thereof, at 200° for 30 min., protected by a calcium chloride tube. The product was allowed to cool, powdered, and recrystallised from the appropriate solvent. The compounds tabulated were prepared. Solvents of crystallisations have been reported for similar compounds.[1,7]

Similarly new N^4N^4-*succinimido-derivatives* were prepared from: sulphadiazine (yield 0·8 g.), m. p. 282° (from acetic acid) (Found: C, 49·4; H, 4·0; N, 14·0; S, 8·5. $C_{14}H_{12}O_4N_4S,C_2H_4O_2$ requires C, 49·0; H, 4·1; N, 14·3; S, 8·2%); sulphaguanidine (2·5 g.), m. p. 248—250° (from water) (Found: C, 42·3; H, 4·4; N, 17·6; S, 10·45. $C_{11}H_{12}O_4N_4S,H_2O$ requires C, 42·0; H, 4·5; N, 17·8; S, 10·2%); sulphamerazine (1·6 g.), m. p. 288—290° (from alcohol) (Found: C, 51·9; H, 4·3; N, 15·8; S, 9·1. $C_{15}H_{14}O_4N_4S$ requires C, 52·0; H 4·05; N, 16·2; S, 9·25%);

[1] Shapiro and Bergmann, *J. Org. Chem.*, 1941, **6**, 774.
[2] Miller, Rock, and Moore, *J. Amer. Chem. Soc.*, 1939, **61**, 1198; Moore and Miller, *ibid.*, 1942, **64**, 1572.
[3] Reid, Reynolds, and Seymour, Herts Pharmaceuticals Ltd., B.P. 595,039/1947; Mayer, *Österr. Chem. Ztg.*, 1951, **52**, 32.
[4] Horii and Yamada, Jap. Patent, 1948, 176,169; *Chem. Abs.*, 1951, **45**, 7145.
[5] Barakat, Shehab, and El-Sadr, *J.*, 1957, 4133.
[6] Picard, Reid, Reynolds, and Seymour, *J.*, 1948, 821.
[7] Vonesch and Velasco, *Arch. Farm. Bioquím. Tucumán*, 1944, I, 241; *Chem. Abs.*, 1945, **39**, 251.

Parent sulpha-compound	Cryst. from	M. p.	Formula	N (%) Found	N (%) Calc.	Yield (%)
N⁴N⁴-Succinoyl derivatives.						
Sulphanilamide ...	AcOH	285° [a]	$C_{10}H_{10}O_4N_2S$	11·3	11·0	55
Sulphathiazole	EtOH	274—275 [b]	$C_{13}H_{11}O_4N_3S_2,C_2H_5{\cdot}OH$	11·2	11·0	52
N⁴N⁴-Phthaloyl derivatives.						
Sulphanilamide ...	C_5H_5N	334—335 [c]	$C_{14}H_{10}O_4N_2S,C_5H_5N$	10·8	11·0	40
Sulphathiazole	AcOH	274—276 [d]	$C_{17}H_{11}O_4N_3S_2$	11·3	10·9	52
Sulphapyridine ...	AcOH	281 [e]	$C_{19}H_{13}O_4N_3S,C_2H_4O_2$	9·65	9·6	48

[a] Lit., 282—283°, 288—289°, 290—290·5°. [b] Lit., 266—267°, 269—270°. [c] Lit., 334°, 320—322°. [d] Lit., 269—269·5°. [e] Lit., 277°, 279—281°, 278—278·5°.

sulphamethazine (1·5 g.), m. p. 256° (from alcohol) (Found: C, 53·1; H, 4·8; N, 15·5; S, 9·45. $C_{16}H_{16}O_4N_4S$ requires C, 53·3; H, 4·4; N, 15·6; S, 8·9%).

The following new *N⁴N⁴-phthalimido-derivatives* were similarly prepared from: sulphadiazine (2 g.), m. p. 318—320° (from pyridine and water) (Found: C, 56·6; H, 3·3; N, 15·1; S, 8·5. $C_{18}H_{12}O_4N_4S$ requires C, 56·8; H, 3·2; N, 14·7; S, 8·4%); sulphamerazine (2·2 g.), m. p. 294—296° (from pyridine and water) (Found: C, 58·2; H, 3·7; N, 14·0; S, 8·05. $C_{19}H_{14}O_4N_4S$ requires C, 57·9; H, 3·55; N, 14·2; S, 8·1%); sulphamethazine (1·8 g.), m. p. 220—222° (from acetic acid) (Found: C, 56·3; H, 4·3; N, 11·8; S, 6·9. $C_{20}H_{16}O_4N_4S,C_2H_4O_2$ requires C, 56·4; H, 4·3; N, 12·0; S, 6·8%).

With adipic acid, under identical conditions, *diamides* (I) were obtained from: sulphanilamide, m. p. 302° (lit.,[8] 287°) (Found: C, 47·2; H, 4·95; N, 11·8; S, 14·0. Calc. for $C_{18}H_{22}O_6N_4S_2$: C, 47·6; H, 4·85; N, 12·3; S, 14·1%); sulphadiazine (0·4 g.), orange (from acetic acid), m. p. 234° (Found: C, 50·6; H, 4·6; N, 16·4; S, 9·4. $C_{26}H_{26}O_6N_8S_2,C_2H_4O_2$ requires C, 50·15; H, 4·5; N, 16·7; S, 9·55%); sulphathiazole (0·5 g.), m. p. 268—270° (from alcohol) (Found: C, 46·35; H, 4·35; N, 12·6; S, 18·9. $C_{24}H_{24}O_6N_6S_4,C_2H_5{\cdot}OH$ requires C, 46·85; H, 4·5; N, 12·6; S, 19·2%).

BIOCHEMISTRY DEPARTMENT, FACULTY OF VETERINARY MEDICINE,
CAIRO UNIVERSITY, GIZA, CAIRO. [*Received, June 4th*, 1957.]

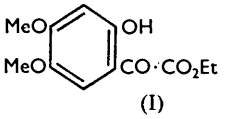
[8] Irani, *Current Sci.*, 1945, **14**, 46.

1022. *A New Synthesis of Abutic Acid.*

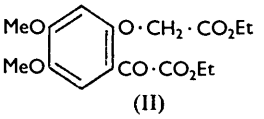
By K. R. HARGREAVES, A. MCGOOKIN, and ALEXANDER ROBERTSON.

AN investigation on the preparation of polyhydroxyphenylglyoxylic acids suggested an alternative route to the synthesis of abutic acid [1] (III; R = R′ = H), which is formed by the oxidation of rotenonic acid,[2] a degradation product of rotenone.

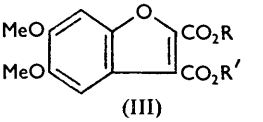
Prepared by the Hoesch reaction from ethyl cyanoformate and 3 : 4-dimethoxyphenol, ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate (I) was condensed with ethyl bromoacetate in potassium carbonate–acetone, yielding the ester (II) which on cyclisation with sodium ethoxide afforded ethyl hydrogen abutate (III; R = H, R′ = Et; or R = Et, R′ = H). Hydrolysis of this ester gave abutic acid, identical with the natural acid and forming methyl abutate,[1] identical with a specimen prepared from the natural acid.



(I)



(II)



(III)

Experimental.—Ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate. Interaction of 3 : 4-dimethoxyphenol (6 g.) and ethyl cyanoformate (6 ml.) by the Hoesch method gave a yellow crystalline

[1] Holton, Parker, and Robertson, *J.*, 1949, 2049.
[2] Takei, Miyajima, and Ono, *Ber.*, 1932, **65**, 1041.

product which separated overnight. This was washed well with ether and warmed on the steam-bath with water (30 ml.) for 20 min., and the resulting solid crystallised from ethanol, giving *ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate* (6·5 g.) in pale yellow needles, m. p. 101°, sparingly soluble in light petroleum and having a green ferric reaction (Found: C, 56·9; H, 5·7. $C_{12}H_{14}O_6$ requires C, 56·6; H, 5·5%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate–light petroleum (b. p. 60—80°) in maroon needles, m. p. 172° (Found: N, 12·6. $C_{18}H_{18}O_9N_4$ requires N, 12·9%).

Ethyl 2-ethoxycarbonylmethoxy-4 : 5-dimethoxyphenylglyoxylate (II). A mixture of ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate (3 g.), acetone (30 ml.), potassium carbonate (10 g.), and ethyl bromoacetate (2·5 g.) was refluxed until a sample did not give a ferric reaction (18 hr.). On isolation and crystallisation from alcohol the product gave *ethyl 2-ethoxycarbonylmethoxy-4 : 5-dimethoxyphenylglyoxylate* in needles (2 g.), m. p. 104°, soluble in ethyl acetate but insoluble in light petroleum (Found: C, 56·3; H, 6·0. $C_{16}H_{20}O_8$ requires C, 56·5; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 201°, from ethyl acetate (Found: N, 10·9. $C_{22}H_{24}O_{11}N_4$ requires N, 10·8%).

Abutic acid (III; R = H, R′ = H). The preceding ester (1·5 g.) in dry alcohol (50 ml.) containing sodium methoxide (from 0·15 g. of sodium) was heated under reflux for ¾ hr., filtered, poured into water (200 ml.), and acidified giving a flocculent precipitate of *ethyl hydrogen abutate* (1·1 g.) which crystallised from ethyl acetate in needles, m. p. 209°, soluble in acetone and sparingly soluble in alcohol or ethyl acetate (Found: C, 56·9; H, 5·0. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

This monoethyl ester (0·5 g.) was hydrolysed with hot 8% aqueous sodium hydroxide (5 ml.) for ½ hr. The resulting abutic acid separated from ethyl acetate in yellow needles (0·3 g.), m. p. 264°, undepressed on admixture with a natural specimen (Found: C, 54·3; H, 4·0. Calc. for $C_{12}H_{10}O_7$: C, 54·1; H, 3·8%). With ethereal diazomethane (10 mols.) for 2 hr. synthetical abutic acid gave the dimethyl ester (0·2 g.) which separated from methanol in needles, m. p. and mixed m. p. 156° (Found: C, 57·2; H, 5·0. Calc. for $C_{14}H_{14}O_7$: C, 57·1; H, 4·8%).

UNIVERSITY OF LIVERPOOL. [*Received, July 1st*, 1957.]

1023. 17β-*Hydroxy*-17α-(3-*hydroxyprop*-1-*ynyl*)*androst*-4-*en*-3-*one*.

By (MISS) S. P. BARTON, G. COOLEY, B. ELLIS, and V. PETROW.

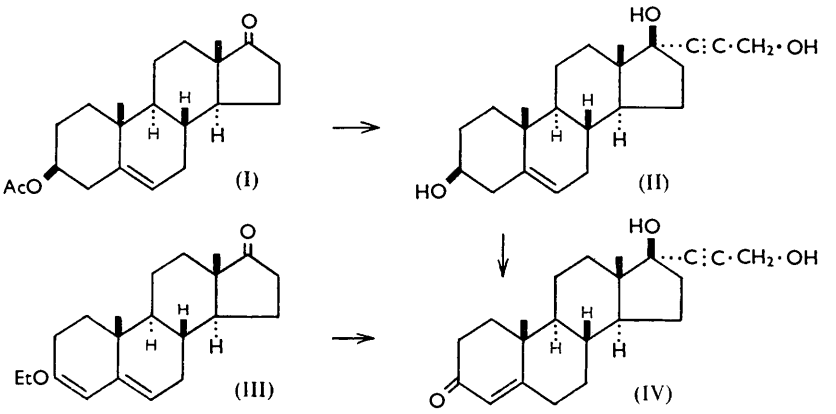
THE compound named in the title was required for biological study as a progestational agent. Condensation of 3β-acetoxyandrost-5-en-17-one (I) with propargyl alcohol in the presence of potassium *tert.*-amyloxide gave 17α-(3-hydroxyprop-1-ynyl)androst-5-ene-3β : 17β-diol (II) [cf. the conversion of 3β-hydroxyandrostan-17-one into 17α-(3-hydroxyprop-1-ynyl)androstane-3β : 17β-diol[1]], also obtained when 3β-(tetrahydro-2-pyranyl)-androst-5-en-17-one [2] was condensed with a Grignard reagent from propargyl tetrahydropyranyl ether [3] and the protective groups were removed from the resulting product. Under mild conditions compound (II) gave a diacetate, under more drastic conditions a triacetate.

Oppenauer oxidation of the triol (II) afforded an αβ-unsaturated ketone (IV). The survival of the primary alcohol group in the acetylenic substituent in these circumstances is noteworthy. Unequivocal confirmation of the structures follows from an alternative partial synthesis of compound (IV) from 3-ethoxyandrosta-3 : 5-dien-17-one (III) by condensation with the Grignard reagent from propargyl tetrahydropyranyl ether and removal of the protective 3- and 17-groups.

Experimental.—$[\alpha]_D$ refer to MeOH solutions in a 1-dm. tube. The ultraviolet absorption spectrum (in ethyl alcohol) was kindly determined by Mr. M. T. Davies, B.Sc.

[1] Wenner and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 24.
[2] Greenhalgh, Henbest, and Jones, *J.*, 1951, 1190; Ott, Murray, and Pederson, *J. Amer. Chem. Soc.*, 1952, **74**, 1239.
[3] Henbest, Jones, and Walls, *J.*, 1950, 3646; Conia, *Bull. Soc. chim. France*, 1955, 1449.

17α-(3-*Hydroxyprop*-1-*ynyl*)*androst*-5-*ene*-3β : 17β-*diol* (II). (*a*) Propargyl alcohol (13 g.) was added to a stirred solution of potassium (22·7 g.) in *tert.*-amyl alcohol (360 ml.) at 70°. When cool, the acetate (I) (23·5 g.) was added, and the mixture stirred for 2 hr. at room temperature and for 2½ hr. at 70°. The *triol* was isolated with ether and, purified from methanol–benzene, formed rods, m. p. 265° (decomp.), $[\alpha]_D^{25}$ −120° (*c* 0·32) (Found: C, 76·0; H, 9·1. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%). Treatment with acetic anhydride–pyridine at room temperature gave 3β-*acetoxy*-17α-(3-*acetoxyprop*-1-*ynyl*)*androst*-5-*en*-17β-*ol*, prisms (from



acetone–hexane), m. p. 131°, $[\alpha]_D^{25}$ −103° (*c* 0·4) (Found: C, 72·4; H, 8·5. $C_{26}H_{36}O_5$ requires C, 72·9; H, 8·5%), but at 100° in 22 hr. gave the *triacetate*, prisms (from acetone–hexane), m. p. 138—139°, $[\alpha]_D^{24}$ −92° (*c* 0·95) (Found: C, 71·4; H, 8·6. $C_{28}H_{38}O_6$ requires C, 71·5; H, 8·1%).

(*b*) A solution of propargyl tetrahydropyranyl ether (7·7 g.) in tetrahydrofuran (100 ml.) was added during 30 min. to a Grignard reagent prepared from magnesium (5 g.) and methyl iodide (20 ml.) in ether (120 ml.). After 30 min., 3β-(tetrahydro-2-pyranyl)androst-5-en-17-one (5 g.) in tetrahydrofuran (100 ml.) was added dropwise during ½ hr., after which the mixture was refluxed for 3½ hr. The complex was decomposed with aqueous ammonium chloride, and the product, isolated with ether, was heated under reflux for 25 min. with toluene-*p*-sulphonic acid (0·25 g.) in ethanol (50 ml.). The solid obtained on the addition of water was crystallised from aqueous pyridine, to give the triol (1·6 g.), identical with a sample prepared by method (*a*) above in m. p. (mixed m. p.) and optical rotation.

17β-*Hydroxy*-17α-(3-*hydroxyprop*-1-*ynyl*)*androst*-4-*en*-3-*one* (IV). (*a*) A solution of the triol (II) (7·2 g.) in toluene (900 ml.) and *cyclo*hexanone (240 ml.) was distilled until 200 ml. of distillate had collected. Aluminium *iso*propoxide (4 g.) in toluene (16 ml.) was then added, and the mixture refluxed for 1½ hr. The *product* was isolated in the usual way, and purified from acetone–hexane. It formed needles, m. p. 204—206°, $[\alpha]_D^{27}$ +3° (*c* 0·56) (Found: C, 77·4; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·1; H, 8·8%), $\lambda_{max.}$ 241 mμ (log ε 4·2).

(*b*) Propargyl tetrahydropyranyl ether (28 g.) in tetrahydrofuran (100 ml.) was slowly added to a Grignard reagent prepared from magnesium (6 g.) and ethyl iodide (20 ml.) in tetrahydrofuran (200 ml.). 30 Min. later, 3-ethoxyandrosta-3 : 5-dien-17-one (2·5 g.) in tetrahydrofuran (100 ml.) was added, and the mixture refluxed for 3 hr. When cool, it was treated with aqueous ammonium chloride and the product isolated with ether. The gummy material in ethanol (100 ml.) was refluxed for 1½ hr. with 2% aqueous oxalic acid (25 ml.), and the product isolated with ether. Chromatography on alumina (30 g.), with ether–benzene (3 : 2) as eluant, gave the ketone (1 g.), needles (from acetone–hexane), b. p. 204°, alone or mixed with a specimen prepared by method (*a*).

Treatment with acetic anhydride–pyridine for 18 hr. at room temperature gave a gum which failed to crystallise. Hydrolysis, however, converted this product into the diol (IV), identified by m. p. and mixed m. p.

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

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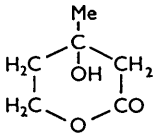
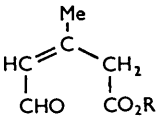
1024. *Studies in Relation to Biosynthesis. Part XII.* The Synthesis of Ethyl 4-Formyl-3-methylbut-3-enoate.*

By A. J. Birch, E. Pride, and Herchel Smith.

We recently suggested that mevalonic lactone (I), which is incorporated *in vitro* in high yield into cholesterol [2] and squalene [3] by systems prepared from rat livers, may function as the precursor of the *iso*pentane unit in natural products by initial conversion into the formyl acid (II; R = H). With the latter as basis a mechanistically plausible scheme for polyisoprenoid or carotenoid synthesis can be developed.[1] The suppression of the incorporation of labelled acetate into cholesterol by the acid (II; R = H) or an ester, readily hydrolysed to it by biological systems, would furnish support for the hypothesis. We have accordingly synthesised the ester (II; R = Et).


(I)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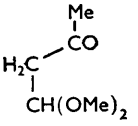
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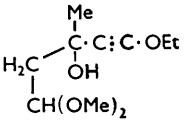
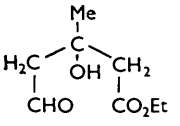

(IV)


(V)

4 : 4-Dimethoxybutan-2-one (III) and ethoxyethynylmagnesium bromide gave the carbinol (IV), which with dilute mineral acid gave, by hydrolysis of the acetal group and hydration of the triple bond, a product consisting largely of the hydroxy-ester (V). Distillation of this over a mixture of tartaric acid and aluminium phosphate afforded the ester (II; R = C_2H_5), whose structure follows from the light absorption [$\lambda_{max.}$ 228 mμ, ε 10,600 (as required for a ββ-disubstituted αβ-unsaturated aldehyde [4]); bands at 1735 and 1684 cm.$^{-1}$ (associated respectively with the saturated ester and αβ-unsaturated aldehyde groupings)].

Experimental.—*1-Ethoxy-5 : 5-dimethoxy-3-methylpent-1-yn-3-ol* (IV). **4 : 4**-Dimethoxybutan-2-one [5] (10 g.) in tetrahydrofuran (50 c.c.) was added with stirring during 30 min. to ethoxyethynylmagnesium bromide [from ethoxyacetylene [6] (9·25 g.) and ethylmagnesium bromide (16·4 g.)] in tetrahydrofuran (100 c.c.) at 0° under nitrogen. The mixture was stirred at room temperature for 4 hr. and then added to ice-cold brine The organic layer was removed and the aqueous layer extracted with ether (3 × 100 c.c.). The combined organic solutions were washed with brine and dried ($MgSO_4$). Distillation and fractionation in a stream of nitrogen gave *1-ethoxy-5 : 5-dimethoxy-3-methylpent-1-yn-3-ol*, b. p. 88°/0·6 mm. (Found: C, 59·6; H, 8·8. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%). The infrared spectrum had bands at 3480 (hydroxyl stretching) and 2275 cm.$^{-1}$ (C≡C stretching).

Ethyl 4-formyl-3-methylbut-3-enoate (II; R = Et). The ethoxypentynol (8 g.) was heated and shaken with 0·2N-sulphuric acid for 5 min. at 100°. The cooled solution was neutralised with sodium hydrogen carbonate and saturated with salt. The product was extracted with ether and heated at 160° (bath temp.) for 10 min. with anhydrous tartaric acid (0·4 g.) and aluminium phosphate [7] (0·4 g.) under slightly reduced pressure. Three distillations (two over a trace of aluminium phosphate) gave *ethyl 4-formyl-3-methylbut-3-enoate* (II; R = Et),

* Part XI, Birch and Massy-Westropp, *J.*, 1957, 2215.

[1] Birch, English, Massy-Westropp, and Smith, *Proc.*, 1957, 233.
[2] Tavormina, Gibbs, and Huff, *J. Amer. Chem. Soc.*, 1956, **78**, 4498.
[3] Cornforth, Cornforth, and Youhotsky-Gore, *Biochem. J.*, 1957, **66**, 10P; Dituri, Gurin, and Rabinowitz, *J. Amer. Chem. Soc.*, 1957, **79**, 79; Amdur, Rilling, and Bloch, *ibid.*, p. 2646.
[4] Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold & Co., London, 1954, p. 97.
[5] Royals and Brannock, *J. Amer. Chem. Soc.*, 1953, **75**, 2050.
[6] Eglington, Jones, Shaw, and Whiting, *J.*, 1954, 1860; Cope and Pike, *Org. Synth.*, 1954, **34**, 46.
[7] Cf. Fisher, *Ber.*, 1943, **76**, 734.

b. p. 67·5°/5 × 10^{-2} mm. (Found: C, 61·3; H, 7·9. $C_8H_{12}O_3$ requires C, 61·5; H, 7·8%), 2 : 4-*Dinitrophenylhydrazone*, m. p. 147° (from ethanol) (Found: C, 49·6; H, 4·9. $C_{14}H_{16}O_6N_4$ requires C, 50·0; H, 4·8%).

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1025. 4- *and* 6-*Methoxy*-2 : 3-*diphenylindole.*

By A. HILARY ORR and MURIEL TOMLINSON.

IT was assumed [1] that the product obtained by heating together benzoin, *m*-aminophenol, and *m*-aminophenol hydrochloride was 6- and not 4-hydroxy-2 : 3-diphenylindole, but no proof of this has yet been given. 7-Chloro-4-methoxy-2 : 3-diphenylindole has now been prepared from 2-chloro-5-methoxyaniline and benzoin, and removal of chlorine from this, by reduction, has given authentic 4-methoxy-2 : 3-diphenylindole, m. p. 147—148°, different from the methyl ether, m. p. 206—207°, obtained by methylation of the above hydroxyindole. The compound, m. p. 206—207°, must therefore be 6-methoxy-2 : 3-diphenylindole.

Experimental.—m-N-(α-*Phenylphenacyl*)*aminophenol*. *m*-Aminophenol (2 g.) and benzoin (4 g.) were heated in an oil-bath at 150—155° until effervescence ceased. The product crystallised in contact with acetic acid and was recrystallised from ethanol, giving m-N-(α-*phenylphenacyl*)*aminophenol* as needles, m. p. 137° (Found: C, 79·0; H, 5·5. $C_{20}H_{17}O_2N$ requires C, 79·2; H, 5·6%). This was unchanged when heated at 200° with either small quantities of hydrochloric acid or *m*-aminophenol hydrochloride, or when boiled in benzene with phosphoric oxide.

6-*Hydroxy*-2 : 3-*diphenylindole* (cf. Ballauf and Schmelzer [1]). Benzoin (5 g.), *m*-aminophenol (6 g.), and *m*-aminophenol hydrochloride (4 g.) were heated at 130—150°, under slightly reduced pressure, until effervescence ceased. Trituration with 10% sodium hydroxide solution afforded the sparingly soluble sodium salt of 6-hydroxy-2 : 3-diphenylindole which was collected, washed, and decomposed with dilute acetic acid. Recrystallisation from acetic acid gave needles, m. p. 145—148°, containing acetic acid which was completely removed only at about 200° (the loss in weight corresponds to ½ mol. of acetic acid). 6-Hydroxy-2 : 3-diphenylindole was left as a glass which, after being powdered, had m. p. 166—167° (Ballauf and Schmelzer report m. p. 168°) (Found: C, 84·3; H, 5·5. Calc. for $C_{20}H_{15}ON$: C, 84·2; H, 5·3%). Methylation was effected in refluxing acetone with 1 equiv. each of methyl sulphate and sodium hydroxide: 6-*methoxy*-2 : 3-*diphenylindole* crystallised from ethanol as prisms, m. p. 206—207° (Found: C, 84·2; H, 5·7. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%); it was unaffected by sodium hydroxide solution. Boiling the phenol with acetic anhydride and anhydrous sodium acetate for 15 min. afforded 6-*acetoxy*-2 : 3-*diphenylindole* which crystallised from acetic acid as needles, m. p. 190° (Found: C, 80·8; H, 5·2. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2%), and gradual addition of benzoyl chloride to a hot solution of the indole in aqueous potassium hydroxide gave 6-*benzoyloxy*-2 : 3-*diphenylindole* which separated from ethanol as needles, m. p. 158° (Found: C, 83·0; H, 5·1. $C_{27}H_{19}O_2N$ requires C, 83·3; H, 4·9%).

7-*Chloro*-4-*methoxy*-2 : 3-*diphenylindole*. 2-Chloro-5-methoxyaniline [2] (1 g.), benzoin (1·3 g.), and a drop of hydrochloric acid heated at 150° afforded 2-*chloro*-5-*methoxy*-N-(α-*phenylphenacyl*)*aniline* which crystallised from ethanol as needles, m. p. 104° (Found: C, 71·6; H, 5·0. $C_{21}H_{18}O_2NCl$ requires C, 71·4; H, 5·1%). Heated with one molar proportion of 2-chloro-5-methoxyaniline hydrochloride at 190°, this gave a gum which was washed with dilute hydrochloric acid and dissolved in benzene. The dried benzene solution was chromatographed on alumina, and the solid so obtained was extracted with hot methanol from which crystallised 7-*chloro*-4-*methoxy*-2 : 3-*diphenylindole* as needles, m. p. 129° (about 50%)

[1] Ballauf and Schmelzer, D.R.P., 533471.
[2] Cummins and Tomlinson, *J.*, 1955, 3475.

(Found: C, 75·7; H, 4·9. $C_{21}H_{16}ONCl$ requires C, 75·6; H, 4·8%). A residue, which did not dissolve, was recrystallised from glacial acetic acid and yielded prisms, m. p. 275—278°, and was presumably αβ-*di*-(2-*chloro*-5-*methoxyanilino*)*stilbene* (Found: C, 68·9; H, 4·8. $C_{28}H_{24}O_2N_2Cl_2$ requires C, 68·4; H, 4·9%).

4-*Methoxy*-2 : 3-*diphenylindole*. A stream of hydrogen was passed through a mixture of 7-chloro-4-methoxy-2 : 3-diphenylindole (0·3 g.) and 10% palladium–charcoal (0·5 g.) in boiling mesitylene (75 c.c.) for 9 hr. The catalyst was then removed by filtration, the solvents were steam-distilled, and the remaining 4-*methoxy*-2 : 3-*diphenylindole* crystallised from ethanol as prisms, m. p. 147—148° (Found: C, 84·0; H, 5·6. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%).

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, July 22nd*, 1957.]

1026. *Spectroscopic Determination of the Stability of Naphthalene Picrate in Chloroform.*

By R. FOSTER.

THE stability constant of naphthalene picrate in chloroform was measured by Moore, Shepherd, and Goodall [1] by a partition method and, expressed as the association constant K = [naphthalene picrate]/([naphthalene][picric acid]), was 2·17 l./mole at 18°. This value is low because no account was taken of the solubility-depression effect of naphthalene in chloroform solution, which lowers the solubility of the picric acid. This effect was fully analysed by Anderson and Hammick,[2] and when it is taken into consideration K = 2·59 l./mole.

Recently Ross and Kuntz [3] determined this association constant spectroscopically by Andrews and Keefer's method [4] to be 0·99 l./mole at 25°. Ross and Kuntz [3] originally suggested that the difference between the spectroscopic and the partition value of K demanded the presence of at least two species of complex. The colorimetric method would measure a coloured complex, such as a charge-transfer complex, whereas the partition method would measure the sum of all types of interaction. Ross, Labes, and Schwarz [5] pointed out that spectroscopy should yield a constant which is the sum of the association constants of all types of association, so that both methods should give the same value for association constant.

Ross and Kuntz's determination, in which chloroform containing 0·75% of alcohol was used, was repeated by the same method, but with pure alcohol-free chloroform. The value of K = 1·1 l./mole at 19° agrees substantially with Ross and Kuntz's, but the method requires that the concentration of one of the components should be very large compared with that of the second. Ross and Kuntz made [naphthalene] $\gg$ [picric acid] and this condition was maintained here. If [picric acid] $\gg$ [naphthalene] complications arise because of the absorption due to the large concentration of free picric acid, and the necessary large but uncertain corrections make any results unreliable.

An important error in the spectroscopic method doubtless arises because the long-wavelength end of the picric acid absorption overlaps the absorption of the naphthalene picrate, in which region obviously the optical measurements must be made. Consequently any shift or alteration in intensity of the free picric acid may seriously affect quantitative measurements which involve the charge-transfer absorption of the complex. The solvent may cause such changes if large amounts of a third component (such as naphthalene) have to be added. In order to minimise these effects, it seems reasonable to take solutions with [naphthalene] = [picric acid]; estimations with this condition give K = 2·4 l./mole

[1] Moore, Shepherd, and Goodall, *J.*, 1931, 1447.
[2] Anderson and Hammick, *J.*, 1950, 1089.
[3] Ross and Kuntz, *J. Amer. Chem. Soc.*, 1954, **76**, 74.
[4] Andrews and Keefer, *ibid.*, 1952, **74**, 1891.
[5] Ross, Labes, and Schwarz, *ibid.*, 1956, **78**, 343.

at 19°, in good agreement with the partition value obtained by Moore, Shepherd, and Goodall.

Experimental.—Materials. " AnalaR " chloroform was washed ten times with distilled water, dried over successive amounts of calcium chloride, and fractionated immediately before use (n_D^{20} 1·4456). Picric acid, recrystallised four times from alcohol, had m. p. 122°. B.D.H. naphthalene, " pure for molecular-weight determinations," was used without further purification (m. p. 80·2°).

Method. If x = molar concentration of the complex (assumed to be 1 : 1, there being no evidence for other species) and A = molar concentration of the picric acid and of the naphthalene originally added then:

$$K = x/(A - x)^2 \simeq x/(A^2 - 2Ax) \text{ if } x \text{ is small}$$

If D is the optical density and ε the extinction coefficient, at a particular wavelength, of the molecular complex then

$$K = \frac{D/\varepsilon}{A^2 - (2AD/\varepsilon)} \text{ or } \frac{A}{D} = \frac{1}{A}\left(\frac{1}{K\varepsilon}\right) + \frac{2}{\varepsilon} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

For a 1 : 1 complex, a plot of A/D against $1/A$ as abscissa should be linear with intercept $2/\varepsilon$ and gradient $1/K\varepsilon$. This is a simplified version of the method used by Ross and Labes.[6]

For $K \approx 2$ l./mole, $x/A \approx 0{\cdot}1$ at $A = 0{\cdot}05$M and $x/A \approx 0{\cdot}01$ at $A = 0{\cdot}005$M: also we have $\varepsilon_{\text{picric acid}}/\varepsilon_{\text{naphthalene picrate}} \approx 0{\cdot}01$ or less at $\lambda \geqslant 420$ mμ. So the measured values of optical density ($\bar{D}$) can be converted into the corrected values (D), corresponding to the absorption due to the complex alone, by subtracting an optical density value (δD) equivalent to the picric acid originally added. These values are obtained from the experimentally confirmed Beer's-law relationships for picric acid alone in chloroform at the various wavelengths used (420—460 mμ). The derived extinction coefficients are given in Table 2.

TABLE 1. *Determination of K from measurements at* 420 mμ.

10^3A(M)	$\bar{D}$	δD	D	$1/A$	A/D	10^3A(M)	$\bar{D}$	δD	D	$1/A$	A/D
54·44	2·123	0·263	1·860	18·4	0·0293	23·82	0·563	0·115	0·448	42·0	0·0532
40·83	1·425	0·198	1·227	24·5	0·0333	20·41	0·429	0·099	0·330	49·0	0·0618
34·02	1·001	0·165	0·836	29·4	0·0407	17·01	0·323	0·082	0·241	58·8	0·0706
30·62	0·882	0·148	0·734	32·7	0·0417	13·61	0·215	0·066	0·149	73·5	0·0913
27·33	0·714	0·132	0·582	36·7	0·0467	10·20	0·134	0·049	0·085	98·0	0·1200

By least-mean-squares from cols. 5 and 6, eqn. (1) becomes $A/D = 0{\cdot}00531 + 0{\cdot}00157(1/A)$ whence $\varepsilon = 377$ and $K = 2{\cdot}29$ l./mole.

TABLE 2. *Summarised results.*

Temp.	Wavelength (mμ)	$\varepsilon_{\text{picric acid}}$	$\varepsilon_{\text{complex}}$	K (l./mole)
19°	420	4·84	377	$2{\cdot}2_9$
19	430	0·152	279	$2{\cdot}5_6$
19	440	0·052	221	$2{\cdot}3_9$
19	450	0·024	152	$2{\cdot}4_6$
19	460	0·014	108	$2{\cdot}2_7$

Mean value for the association constant of naphthalene–picric acid in chloroform at 19° = 2·4 l./mole.

Individual naphthalene and picric acid solutions were made up separately and appropriate volumes taken to make an equimolar solution. This was diluted to make the individual solutions. Optical measurements were made on solutions in 1 cm. stoppered fused silica cells by using a Unicam S.P. 500 spectrophotometer. Full details of one determination are given in Table 1. All the plots of A/D against $1/A$ give good straight lines. The results are summarised in Table 2.

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QUEEN'S COLLEGE (UNIVERSITY OF ST. ANDREWS), DUNDEE. [*Received, July* 31*st*, 1957.]

[6] Ross and Labes, *J. Amer. Chem. Soc.*, 1957, **79**, 76.