Journal of Organometallic Chemistry, 212 (1981) 1—9
Elsevier Sequoia S.A., Lausanne — Printed in The Netherlands

LITHIATION REACTIONS OF 1-(2'-BROMOPHENYL)PYRROLE AND RELATED COMPOUNDS

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(Received November 24th, 1980)

Summary

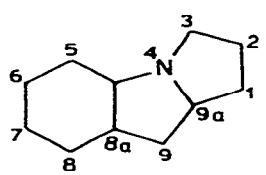
9-Keto-9H-pyrrolo[1,2-*a*]indole is formed by the intramolecular cyclisation of the dilithio derivatives generated from either 1-(2'-carboxyphenyl)pyrrole or 1-(2'-bromophenyl)pyrrole-2-carboxylic acid. The reaction of the 2'-lithio derivative of 1-phenylpyrrole with various electrophiles is also described.

Introduction

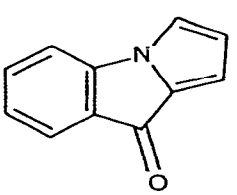
Considerable interest has been shown in the pyrrolo[1,2-*a*]indole ring system (I) [1] which forms the skeleton of the mitomycins, a small group of naturally-occurring pyrroloindoles exhibiting both antibacterial and antitumour activity.

Several syntheses have been reported wherein bond formation is achieved between C(8a)—C(9) [2a,b] or C(9)—C(9a) [2c,d,e] under Friedel—Crafts or acidic conditions. The present study describes the synthesis of 9-keto-9H-pyrrolo[1,2-*a*]indole (II) via the anionic equivalent of the Friedel—Crafts cycloacylation [3a].

In addition, 2'-lithio-1-phenylpyrrole (III) is shown to be a useful synthetic intermediate which reacts with a variety of electrophiles.



(I)



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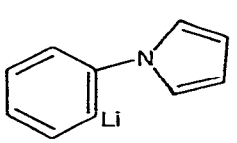

(III)

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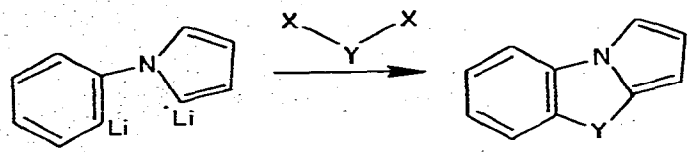
Discussion

A previous paper [4] described the synthesis of pyrrolo[1,2-*a*]indole analogues (V) from 2,2′-dilithio-1-phenylpyrrole (IV) (eq. 1). Difunctional carbon



(1)

(IV) (V)

X = Hal

Y = $SiPh_2$, $GeMe_2$, PPh, AsPh

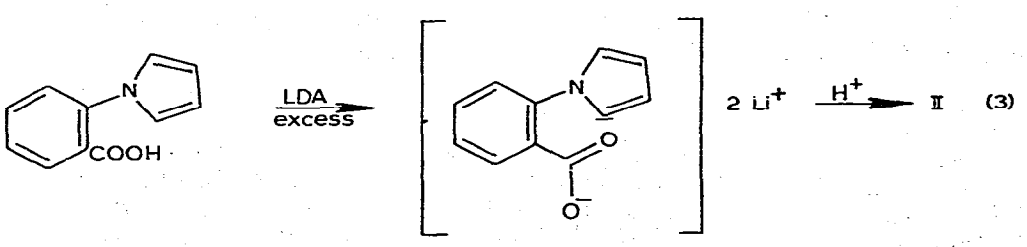
electrophiles failed to react with IV in the expected manner, replacing only the more reactive benzenoid lithium. Thus reaction of the dianion (IV) with chloroformate esters, $ClCO_2R$ (R = Et, Ph) gave the intermediate 2′-carboxy-ethyl and -phenyl pyrroles, respectively (eq. 2). In the reaction with phenyl chloroformate however, a small amount of II (6%) was obtained.

(2)

(VI)

(a)	R = Et	17%	–
(b)	R = Ph	19%	6%

The ketone II was first obtained as a minor product in the lithiation and subsequent carboxylation of 1-phenylpyrrole [5]. Presumably, cyclisation proceeded via the intermediate dianion VIII. In the present study, VIII was generated from 1-(2′-carboxyphenyl)pyrrole (VII) using an excess of lithium diisopropylamide (LDA). Intramolecular cyclisation gave the ketone II in moderate yield (eq. 3).



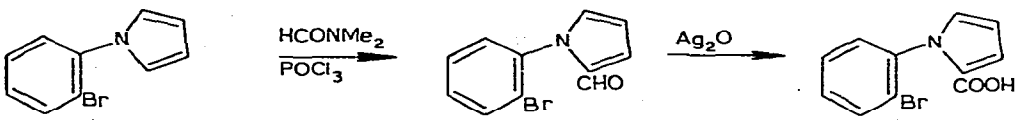
(3)

(VII) (VIII)

Similar treatment of the ester VIa with LDA (1 mol or excess) was unsatisfactory, giving poor yields of II (1—7%), accompanied by extensive tar formation.

A second route to the ketone II was available through cyclisation of the acid

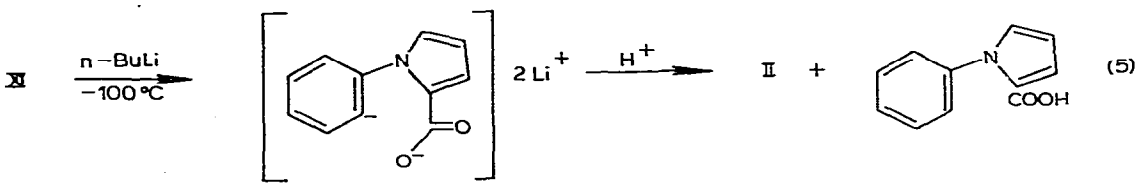
XI. Vilsmeier formylation [6] of 1-(2′-bromophenyl)pyrrole (IX) gave the aldehyde X and oxidation with silver oxide [7] afforded the acid XI in good yield (eq. 4).



(4)

(IX) (X) (XI)

Reaction of XI with n-butyllithium at −100°C [3a,b] gave the intermediate dianion XII which cyclised to give the ketone II (eq. 5). "Debrominated acid" (XIII) was obtained as a by-product of the reaction.

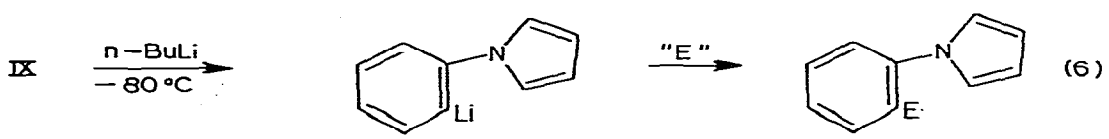


(5)

(XII) (XIII)

The dianion XII failed to react with electrophiles such as benzophenone or ethyl bromoacetate. Instead, the product of intramolecular reaction (II) as well as the acid XIII was obtained.

Whereas the dianion IV is readily formed from 1-(2′-bromophenyl)pyrrole (IX) at 0°C [4], 2′-lithio-1-phenylpyrrole (III) can be selectively generated at −80°C. Reaction of the anion III with a variety of electrophiles (eq. 6) led to a range of products in fair to good yield (Table 1).

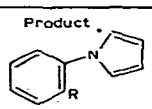


(6)

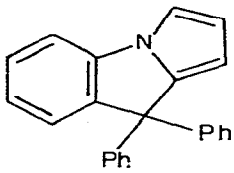
(III) (XIV)

TABLE 1

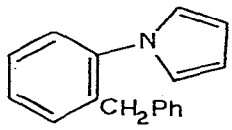
REACTIONS OF 2′-LITHIO-1-PHENYLPYRROLE (III) WITH ELECTROPHILES (eq. 6)

Electrophile	Product 		Isolated yield (%)
	R	No.	
Benzophenone	$C(OH)Ph_2$	XV	72
Benzaldehyde	CH(OH)Ph	XVII	68
Benzoyl chloride	COPh	XIX	16
Benzonitrile	C=NHPh	XX	67
Ethyl chloroformate	CO_2Et	VIa	52
Phenyl chloroformate	CO_2Ph	VIb	19

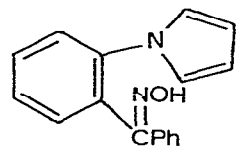
The benzophenone adduct XV gave the pyrrolo[1,2-*a*]indole (XVI) on treatment with perchloric acid [8]. However, the benzaldehyde adduct XVII did not cyclise under similar conditions but probably reacted by intermolecular hydride transfer to give the corresponding hydrocarbon XVIII and ketone XIX. The mass spectrum of XVII suggests that a similar intermolecular reaction occurs in the mass spectrometer.



(XVI)



(XVII)



(XXI)

The benzaldehyde adduct XVII was readily oxidised to the ketone XIX with pyridinium dichromate [9]. Reaction of III with benzoyl chloride gave the ketone XIX in poor yield and preparation of XIX from 2,5-dimethoxytetrahydrofuran and 2-aminobenzophenone [10] also proved unsatisfactory. The imine XX obtained from the reaction of III with benzonitrile did not give the ketone XIX on hydrolysis, but was readily converted to the oxime XXI.

Ethyl and phenyl chloroformate reacted with III at −80° C to give the corresponding esters VIa and VIb, respectively. In both cases there was extensive intermolecular reaction of the intermediates resulting in dimeric and oligomeric products.

Experimental

M.p.'s were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Unicam SP 200 spectrometer for potassium bromide discs, unless otherwise specified. ^{1}H NMR spectra were recorded at 60 MHz on a Perkin—Elmer R12B spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded at 70 eV on an AEI MS 30 mass spectrometer. Column chromatography was carried out with Merck silica gel 60, particle size 0.063—0.200 mm, 70—230 mesh ASTM, catalogue no. 7734. All reactions involving organolithium reagents were performed under dry nitrogen in a 2-necked round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and rubber serum cap. Tetrahydrofuran was dried by distilling from sodium benzophenone ketyl. Diisopropylamine was distilled from calcium hydride .

Cyclisation of 1-(2′-carboxyphenyl)pyrrole (VII)

A solution of 1-(2′-carboxyphenyl)pyrrole (VII) [2d] (1.56 g, 8.32 mmol) in dry THF (20 ml) was added dropwise to a cold solution (0° C) of lithium diisopropylamide (33 mmol) (prepared from diisopropylamine (4.69 ml, 33 mmol) in dry THF (30 ml) and n-butyllithium (17.9 ml of a 1.86 *M* solution in hexane, 33 mmol)). The solution was stirred at 0° C for 30 min and 40—50° C for 22 h. The dark coloured reaction mixture was poured into 1 *M* hydrochloric acid (85 ml) and extracted with chloroform (2 × 30 ml). The organic layer was

extracted with aqueous potassium hydroxide, dried and the solvent evaporated giving the crude ketone II. Sublimation (90—100°C/0.5 mmHg) gave II in 59% yield (0.84 g), m.p. 118—120°C (lit. [2d] 121—122°C). Anal. Found: C, 77.9; H, 4.5; N, 7.9. $C_{11}H_7NO$ calcd.: C, 78.1; H, 4.2; N, 8.3%. ν_{max}: 1670s (C=O) cm^{-1}. $\delta(CDCl_3)$: 6.8—7.6 (m, 5 H, benzenoid H and H(3)), 6.7 (m, 1 H, H(1)), 6.2 (m, 1 H, H(2)). *m/e* 169 (100%, M^+), 141 (16%, $M^+ - CO$), 114 (47%, $M^+ - C_2HNO$). Hydrazone, m.p. 169—170°C (lit. [2d] 171.4—172.2°C). Anal. Found: C, 72.1; H, 5.0; N, 22.7. $C_{11}H_9N_3$ calcd.: C, 72.1; H, 5.0; N, 22.9%.

1-(2'-Bromophenyl)-2-pyrrolealdehyde (X)

1-(2'-Bromophenyl)pyrrole (IX) (79.5 g, 0.36 mol) was formylated [6] giving the 2-pyrrolealdehyde. Trituration of the crude product with diethyl ether gave chromatographically pure yellow solid (58.1 g, 65%), and analytically pure material, m.p. 102—109°C, was obtained by recrystallisation from diethyl ether. Anal.: Found: C, 52.8; H, 3.1; N, 5.5. $C_{11}H_8BrNO$ calcd.: C, 52.8; H, 3.2; N, 5.6%. ν_{max}: 2750m (aldehyde C—H), 1660s (C=O) cm^{-1}. $\delta(CDCl_3)$: 9.5 (s, 1 H, aldehyde H), 7.2—7.8 (m, 4 H, benzenoid H), 7.1 (dd, 1 H, H(5)), 6.9 (m, 1 H, H(3)), 6.4 (dd, 1 H, H(4)). *m/e* 249 (24%, M^+ [^{79}Br]), 170 (100%, $M^+ - Br$), 141 (8%, $M^+ - Br - CHO$).

1-(2'-Bromophenyl)pyrrole-2-carboxylic acid (XI)

A solution of the 2-pyrrolealdehyde (X) (15.0 g, 0.06 mol) in ethanol (400 ml) was basified with sodium hydroxide (4.8 g, 0.12 mol) in 80% ethanol (50 ml). Freshly prepared silver oxide [7] (20.4 g, 0.12 mol) was added and the suspension was stirred, with protection from light, at room temperature for 23 h.

The precipitate was filtered off and the filtrate evaporated to dryness, giving a white residue which was taken up in water (170 ml) and extracted with ether (3 × 100 ml). The aqueous layer was acidified with hydrochloric acid (5 *M*) and extracted with ether (3 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated giving a chromatographically pure white solid (14.8 g; 93%). Recrystallisation from diethyl ether gave the analytically pure acid, m.p. 167—173°C. Anal. Found: C, 49.3; H, 3.0; N, 5.3. $C_{11}H_8BrNO_2$ calcd.: C, 49.6; H, 3.0; N, 5.3%. ν_{max}: 2900(br) (acid O—H), 1670s (C=O) cm^{-1}. $\delta(CDCl_3/(CD_3)_2CO)$: 7.3—7.7 (m, 4 H, benzenoid H), 7.0 (dd, 1 H, H(5)), 6.8 (m, 1 H, H(3)), 6.2 (m, 1 H, H(4)), *m/e*: 265 (67%, M^+ [^{79}Br]); 221 (11%, $M^+ - CO_2$), 186 (100%, $M^+ - Br$).

Cyclisation of 1-(2'-bromophenyl)pyrrole-2-carboxylic acid (XI)

n-Butyllithium (4.0 ml of 1.85 *M* solution in hexane, 7.53 mmol) was slowly added (1 h) to a solution of XI (1.00 g, 3.76 mmol) in dry THF (25 ml). The temperature was maintained at ~—100°C by a liquid nitrogen/diethyl ether bath. The orange solution was then allowed to warm to —20°C for 2 h and was poured into 5% hydrochloric acid (70 ml). The mixture was extracted with chloroform (2 × 50 ml) and the chloroform extracts were washed with 10% aqueous sodium hydroxide. Acidification of the alkaline extract and extraction with diethyl ether (3 × 30 ml) gave the crude "debrominated acid" XIII (0.26 g). Recrystallisation from benzene gave a white solid (0.095 g, 13%), m.p.

168—169°C (lit. [11] 166°C and [5] 183—183—184°C). Anal. Found: C, 70.8, H 4.8; N, 7.3. $C_{11}H_9NO_2$ calcd.: C, 70.6; H, 4.8; N, 7.5%.

The solid obtained from the chloroform extract was chromatographed on silica gel (35 g) using chloroform as eluent. The pyrrolo[1,2-*a*]indole (II) (0.27 g, 42%) thus obtained was recrystallised from chloroform/cyclohexane.

Preparation of 2'-lithio-1-phenylpyrrole (III)

2'-Lithio-1-phenylpyrrole (III) was prepared by the addition of a standard solution of n-butyllithium (10% molar excess) in n-hexane to a stirred, cooled solution (—80°C) of 1-(2'-bromophenyl)pyrrole (IX) (0.01—0.04 mol) in dry THF (25—60 ml). After stirring at —80°C for 30 min, the yellow suspension was employed as described below.

Reactions of III with electrophiles (Table 1)

A. With benzophenone. To a stirred suspension of 2'-lithio-1-phenylpyrrole (III) (15.4 mmol) in dry THF (25 ml) at —80°C was added under nitrogen a solution of benzophenone (2.81 g, 15.4 mmol) in dry THF (25 ml). The resulting clear yellow solution was stirred at —80°C for 2 h and then poured on to crushed ice (150 g) and extracted with chloroform (3 × 70 ml). The chloroform extracts were combined, dried and the solvent removed, giving a yellow oil (6.13 g) which was chromatographed on silica gel (160 g) using n-hexane/benzene mixtures. The carbinol (XV) was obtained as a yellowish oil (3.62 g, 72%) which was distilled (220°C/0.1 mmHg) in a Kugelrohr tube. A satisfactory analysis was not obtained. ν_{max} (film): 3530s (O—H) cm^{-1}; $\delta(CDCl_3)$: 7.0—7.4 (m, 14 H, benzenoid H), 6.2 (m, 2 H, H(2) and H(5)), 6.0 (m, 2 H, H(3) and H(4)), 2.8 (s, 1 H, O—H, exchangeable with D_2O). *m/e* 325 (100%, M^+), 307 (44%, $M^+ - H_2O$), 230 (48%, $M^+ - H_2O - C_6H_5$).

Cyclisation of XV was effected by treating a solution of the carbinol (0.80 g, 2.47 mmol) in dry nitromethane (12 ml) with a few drops of 72% perchloric acid [8]. The solution was stirred at room temperature for 4 h. Saturated potassium bicarbonate (50 ml) was then added and extraction was performed with chloroform (2 × 30 ml). The organic layer was dried and the solvent evaporated giving an orange oil which was chromatographed on silica gel (70 g), elution being performed with n-hexane/benzene mixtures. The product, 9,9-diphenyl-9H-pyrrolo[1,2-*a*]indole (XVI) was obtained as a white crystalline solid (0.458 g, 60%), m.p. 132—134°C, which was recrystallised from n-hexane. Anal.: Found: C, 89.6; H, 5.6; N, 4.4. $C_{23}H_{17}N$ calcd.: C, 89.9; H, 5.5; N, 4.6%. ν_{max}: 1605m, 1590m, 1500s, 1470m (ar C=C), 750s, 690s (ar C—H), cm^{-1}. $\delta(CDCl_3)$: 6.9—7.4 (m, 15H, benzenoid H and H(3)), 6.4 (m, J ~4Hz, 1 H, H(2)), 6.1 (dd, J ~4 Hz and 1 Hz, 1 H, H(1)). *m/e* 307 (100%, M^+), 230 (97%, $M^+ - C_6H_5$).

B. With benzaldehyde. To a stirred suspension of III (40.7 mmol) in dry THF (60 ml) at —80°C was added under nitrogen a solution of benzaldehyde (freshly distilled, 4.74 g, 44.7 mmol) in dry THF (30 ml). The solution was stirred at —80°C for 1 h and 0°C for 3½ h and then poured into water (100 ml) and extracted with chloroform (3 × 50 ml). The chloroform extracts were dried and the solvent evaporated giving an orange oil (10.9 g) which was chromatographed on silica gel (220 g) using benzene followed by chloroform as eluents.

The adduct XVII (9.84 g) was purified further by distillation (120—150°C/0.05 mmHg) giving a yellow oil (68%). Anal.: Found: C, 81.4; H, 6.0; N, 5.6. $C_{17}H_{15}NO$ calcd.: C, 81.9; H, 6.0; N, 5.6%. ν_{max} (film): 3300s (br) (O—H) cm^{-1}. $\delta(CDCl_3)$ 7.0—7.6 (m, 9 H, benzenoid H), 6.6 (m, 2 H, H(2), and H(5)), 6.2 (m, 2 H, H(3) and H(4)), 5.2 (s, 1 H, CH(OH)Ph), 2.3 (s, 1 H, O—H, exchangeable with D_2O). *m/e* 170 (100%, $M^+_{XIX} - C_6H_5$), 156 (70%, $M^+_{XVIII} - C_6H_5$), 142 (12%, $M^+_{XVIII/XIX} - CO/CH_2$).

The benzaldehyde adduct XVII (1.33 g, 5.32 mmol) in dry methylene chloride (9 ml) was stirred with pyridinium dichromate [9] (3.077 g) under nitrogen at room temperature for 27 h. The reaction mixture was diluted with methylene chloride, filtered and the residue washed well with methylene chloride. Removal of the solvent gave a darkly-coloured solid which was chromatographed on silica gel (40 g) using chloform as eluent. The ketone XIX was obtained as a pale-yellow solid (0.79 g, 61%), m.p. 100—101°C, which was recrystallised from ether. Anal.: Found: C, 82.6, H, 5.3; N, 5.7. $C_{17}H_{13}NO$ calcd.: C, 82.6; H, 5.3; N, 5.7%. ν_{max}: 1660s (C=O) cm^{-1}. $\delta(CDCl_3)$: 7.1—7.7 (m, 9 H, benzenoid H), 6.7 (m, 2 H, H(2) and H(5)), 5.9 (m, 2 H, H(3) and H(4)). *m/e* 247 (41%, M^+), 198 (100%, $M^+ - CO - H$), 170 (6%, $M^+ - C_6H_5$).

C. With benzoyl chloride. In a two-necked flask fitted with a separating funnel, a solution of benzoyl chloride (1.73 g, 12.3 mmol) in dry THF (30 ml) was cooled under nitrogen to —80°C. In a separate two-necked flask at —80°C a solution of 2′-lithio-1-phenylpyrrole (III), was prepared from IX (2.73 g, 12.3 mmol) in dry THF (45 ml) and n-butyllithium (25.8 mmol of a 1.86 *M* solution in hexane). The solution of III was transferred to the separating funnel using a double-tipped needle and added over 40 min to the benzoyl chloride solution. Stirring was continued at —80°C for 4 h. The reaction was quenched with water (2 × 10 ml), diluted with chloroform (40 ml) and stirred with 1 *M* potassium hydroxide (50 ml) for 15 min. After extraction with chloroform (3 × 30 ml) and evaporation, the crude product was chromatographed on silica gel (120 g) using benzene as eluent. The darkly-coloured solid thus obtained (0.99 g, 32%) was purified further by preparative thin-layer chromatography with benzene as eluent. The ketone XIX was isolated as a pale yellow solid (0.51 g, 16%).

D. With benzonitrile. A solution of benzonitrile (1.47 g, 14.0 mmol) in dry THF (20 ml) was added over 10 min under nitrogen to a stirred suspension of 2′-lithio-1-phenylpyrrole (III) (12.5 mmol) in dry THF (25 ml) at —80°C. The orange solution was stirred at —80°C for 1 h and then at room temperature for $2\frac{1}{2}$ h. The reaction was quenched by stirring with ammonium chloride (1 g) in water (50 ml) for 1 h. Extraction with ether (2 × 30 ml) followed by evaporation of the solvent gave an orange oil (3.29 g) which was chromatographed on silica gel (120 g) using petroleum ether/ether 1/1 as eluent. The imine XX (2.07 g, 67%) was obtained as a yellow oil which crystallised on standing. Bulb-to-bulb distillation (140—160°C/0.5 mmHg) afforded an oil which did not give a satisfactory analysis. ν_{max}: 3250m (N—H), 1600s (C=N) cm^{-1}. $\delta(CDCl_3)$ 8.8(br) (s, 1 H, N—H, exchangeable with D_2O), 7.2—7.7 (m, 9 H, benzenoid H), 6.7 (m, 2 H, H(2) and H(5)), 6.0 (m, 2 H, H(3) and H(4)). *m/e* 245 (100%, $M^+ - 1$), 169 (9%, $M^+ - C_6H_5$).

Oximation of the imine XX (0.80 g, 3.25 mmol) was effected by refluxing

with hydroxylamine hydrochloride (0.55 g) and sodium acetate (hydrate) (1.49 g) in 70% aqueous ethanol (40 ml) for 15 h. The solvent was evaporated and the residue was taken up in water (50 ml). Extraction with ether (2 × 50 ml) followed by evaporation gave a yellow solid. Recrystallisation from methanol afforded the oxime XXI as yellow needles (0.36 g, 42%), m.p. 140—142°C. Anal.: Found: C, 78.2; H, 5.4; N, 10.7. $C_{17}H_{14}N_2O$ calcd.: C, 77.9; H, 5.3; N, 10.7%. ν_{max}: 3250(br) (O—H), 1620w (C=N) cm^{-1}. $\delta(CDCl_3)$: 7.1—7.6 (m, 10 H, benzenoid H and O—H); 6.8 (m, 2 H, H(2) and H(5)), 6.1 (m, 2 H, H(3) and H(4)). *m/e* 262 (2%, M^+); 245 (100%, $M^+ - OH$), 244 (86%, $M^+ - H_2O$), 230 (8%, $M^+ - H_2O - N$).

F. With ethyl chloroformate. The reaction was effected as described above for benzoyl chloride. 2′-Lithio-1-phenylpyrrole (III) (9.43 mmol) in dry THF (18 ml) was added to ethyl chloroformate (1.36 g, 12.5 mmol) in dry THF (15 ml) and stirring was continued at −80°C for 1 h. The reaction solution was then poured onto crushed ice (150 g) containing dilute hydrochloric acid (30 ml). Extraction with chloroform (2 × 50 ml) and evaporation gave a dark-coloured oil which was chromatographed on silica gel (120 g) using benzene as eluent. The ester VIa was obtained as an orange oil (1.06 g, 52%) which was identical by IR, NMR and mass spectroscopy with an authentic sample of VIa (b.p. 121°C/0.5 mmHg) prepared according to the usual method [2d] in 68% yield. Anal.: Found: C, 72.4; H, 6.1; N, 6.6. $C_{13}H_{13}NO_2$ calcd.: C, 72.6; H, 6.1; N, 6.5%. ν_{max} (film): 1720s (C=O) cm^{-1}. $\delta(CDCl_3)$: 7.2—7.9 (m, 4 H, benzenoid H), 6.8 (m, 2 H, H(2) and H(5)), 6.3 (m, 2 H, H(3) and H(4)); 4.2 (q, 2 H, CO_2CH_2), 1.1 (t, 3 H, CH_3). *m/e* 215 (57%, M^+), 170 (21%, $M^+ - CO_2$), 143 (100%, $M^+ - CO_2C_2H_5$).

G. With phenyl chloroformate. The reaction was carried out as described above for benzoyl chloride. 2′-Lithio-1-phenylpyrrole (III) (9.63 mmol) in dry THF (35 ml) was added to phenyl chloroformate (2.06 g, 13.1 mmol) in dry THF (20 ml). After stirring at −80°C for 1 h and 0°C for 1 h the dark-coloured mixture was poured onto crushed ice (150 g) and extracted with chloroform (2 × 60 ml). After evaporation of the solvent the crude product was chromatographed on silica gel (220 g), elution being performed with benzene/chloroform mixtures. The phenyl ester VIb was isolated as a brownish oil (0.48 g, 19%) which was not purified further. ν_{max}: 1730 (C=O) cm^{-1}. $\delta(CDCl_3)$: 7.0—7.6 (m, 9 H, benzenoid H), 6.9 (m, 2 H, H(2) and H(5)), 6.3 (m, 2 H, H(3) and H(4)), *m/e* 169 (91%, $M^+ - C_6H_6O$), 143 (25%, $M^+ - CO_2C_6H_5$), 77 (100%, $C_6H_5^+$).

In addition, the ketone II was isolated in 6% yield (0.13 g).

Acknowledgements

We thank Queen Elizabeth College for the award of a Student Demonstratorship (to M.E.K.C.) which made the work possible, and the University of London Intercollegiate Research Services Scheme at the School of Pharmacy for some of the analyses.

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