Reaction of 4-Benzylidene-1-butylpyrrolidine-2,3-diones with Aromatic Thiols and Amines

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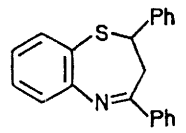
2-Butyl-4-arylpyrrolo[*c*][1,5]benzothiazepin-1(2*H*)-ones are prepared by the reaction of 2-aminobenzenethiol with 1-butyl-4-arylidenepyrrolidine-2,3-diones. These ketones also react with simple thiols to give normal 1,4-addition products. In addition they react with aniline to give a mixture of substituted benzylideneanilines, 1-butyl-3-arylamino-4-(α-arylaminobenzyl)-3-pyrrolin-2-ones and 1-butyl-3-arylamino-3-pyrrolin-2-ones.

CHALCONE and its analogues react with 2-aminobenzenethiol to give 2,3,6,7-tetrahydro-1,4-thiazepines (I).[1,2] Base catalysis is needed to effect addition between the double bond and the thiol, followed by acidic conditions for the condensation of the amino and carbonyl groups.

(I)



We now report the reaction of other αβ-unsaturated ketones namely the 4-arylidene-1-butylpyrrolidine-2 3-diones (II) with 2-aminobenzenethiol to give a similar heterocyclic nucleus (III). Unlike the chalcones the αβ-unsaturated ketones (II) reacted readily with 2-aminobenzenethiol in the absence of catalysts to give the pyrrolo[3,4-*c*]benzothiazepinones (III).

Reaction of a primary amine with the 3-keto-position of a pyrrolidine-2 3-dione generally results in the formation of a 3-pyrrolin-2-one.[3-6] Our spectroscopic evidence demonstrates that a similar bond migration occurs in our reactions. The n.m.r. results were best interpreted on the basis of a structure of type (III) resulting from the reaction of the SH and NH_2 groups of the 2-aminobenzenethiol with the double bond and the 3-keto-groups respectively of the αβ-unsaturated ketone. As additional evidence of the sulphide structure of the heterocycles (III) a sulphone could be formed from (IIIb) by oxidation with hydrogen peroxide–glacial acetic acid.

4-Benzylidene-1-butylpyrrolidine-2,3-dione (IIa) underwent the normal base-catalysed reactions of αβ-unsaturated ketones with thiols to give the sulphides (IV) and (V). Evidence from n.m.r. spectroscopy and the violet colour developed with ferric chloride indicated an enolic structure for these compounds. Previous workers have shown 4-substituted pyrrolidine-2,3-diones exist invariably in the enolic rather than the ketonic form.[4,7,8] When heated gently under reflux with 2-aminobenzenethiol, 4-(α-benzylthiobenzyl)-1-butyl-3-hydroxy-3-pyrrolin-2-one (V) gave the corresponding seven-membered heterocycle (IIIa) (Scheme).

Attempts were made to add aniline to the double bond of 4-benzylidene-1-butylpyrrolidine-2,3-dione to prepare analogues of the thiol adducts (IV) and (V). Although several basic and acidic catalysts were tried without success, it was found that a reaction could be

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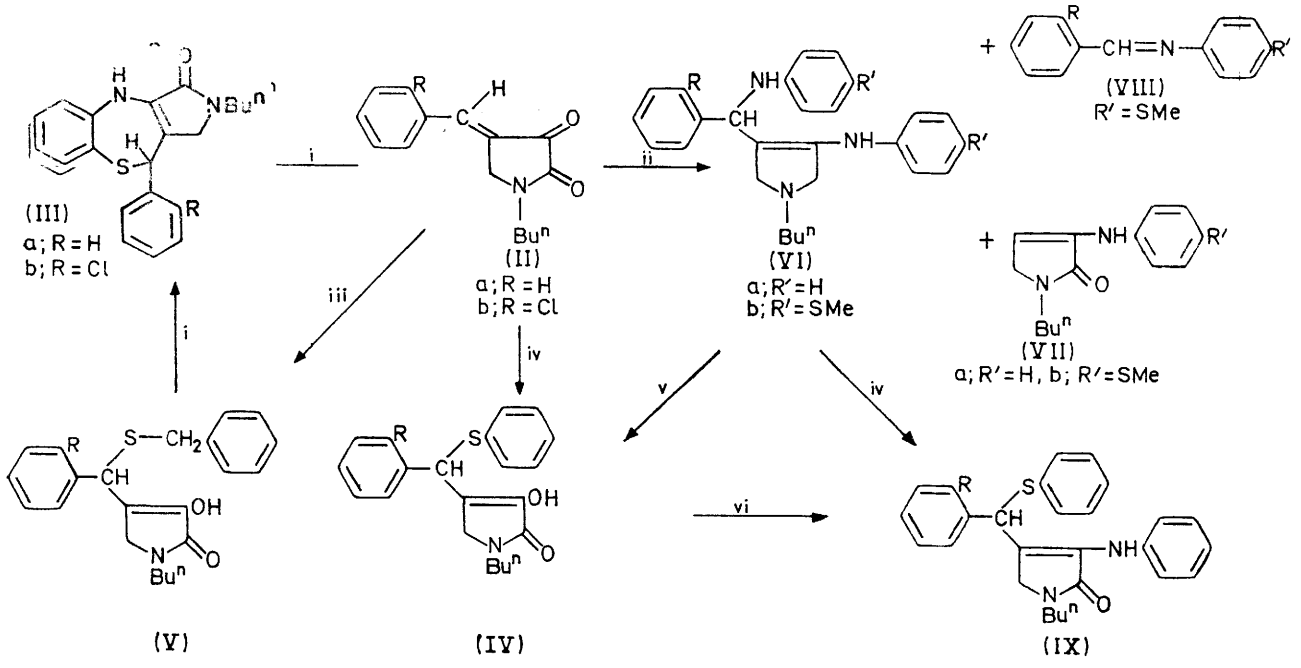
promoted by heating the ketone under reflux with an excess of aniline to yield compounds (VIa), (VIIa), and (VIIIa).

N-Substituted-3-arylamino-3-pyrrolin-2-ones (VII) have been described previously by Southwick *et al.*[3] who prepared them by a condensation between aniline and an *N*-substituted-pyrrolidine-2,3-dione. The second reaction product, benzylideneaniline (VIIIa) could not be obtained pure due to large quantities of tarry by-products; its presence was, however, inferred by hydrolysis of the reaction mixture with dilute hydrochloric acid and subsequent reaction to give benzaldehyde 2,4-dinitrophenylhydrazone. When the reaction was repeated with 4-aminothioanisole instead of aniline, pure *N*-benzylidene-*p*-methylthioaniline (VIIIb) was isolated.

The diamino-derivatives, 3-arylamino-4-(α-aryl-aminobenzyl)-3-pyrrolin-2-one (VI) have not been described before. N.m.r. and i.r. spectra of (VIa) indicate that the amino-function at the 3 position of the ring is an enamine and not an imine. Many other 3-amino-derivatives of 3-pyrrolin-2-ones possess this structural feature.[3-5]

If 4-benzylidene-1-butylpyrrolidine-2,3-dione (IIa) was regarded as a simple αβ-unsaturated ketone, the reaction with an aromatic amine would be expected to yield the normal amine adduct. However, the 3-keto-group of such a compound would no longer be conjugated with the double bond and in the presence of an excess of amine would readily condense with further aromatic amine to yield the diamine (VI). The ease of this latter type of reaction has been demonstrated in pyrrolidine-2,3-diones of similar structure.[3,4] At the same stage during the formation of the diamine (VI) it is evident that some of the compound underwent a disproportionation to yield (VII) and (VIII) since (VI) itself is stable to the action of further amine under the conditions of the reaction.

When heated under reflux with an excess of benzenethiol in the presence of piperidine, 3-anilino-4-(α-anilinobenzyl)-1-butyl-3-pyrrolin-2-one (VIa) underwent a nucleophilic displacement to give 3-anilino-1-butyl-4-(α-phenylthiobenzyl)-3-pyrrolin-2-one (IX). This latter compound was also prepared from 4-benzylidene-1-butylpyrrolidine-2,3-dione (IIa) by an alternative route in which the intermediate sulphide (IV) was treated with a four-fold excess of an equimolar mixture of aniline and formic acid to give the thio-derivative (IX) in 51% yield. There are literature reports of other *N*-substituted-3-hydroxy-3-pyrrolin-2-ones reacting under similar conditions with amines.[6,7] When heated under reflux with an excess of aniline for a short period the phenylthio-group of (IV) was displaced to give the pyrrolinone (VIa).



SCHEME

Reagents: i, 2-aminobenzenethiol; ii, excess of aromatic amine; iii, toluene-α-thiol–piperidine; iv, thiophenol–piperidine; v, excess of aniline; vi, aniline–formic acid.

EXPERIMENTAL

M.p.s were taken on a Büchi apparatus. The i.r. spectra were taken for Nujol mulls. ^{1}H N.m.r. spectra were taken for solutions in deuteriochloroform with tetramethylsilane as internal standard at 100 MHz.

4-Benzylidene-1-butylpyrrolidine-2,3-dione (IIa).—This compound was prepared by Southwick and Barnas's method [7] from ethyl 1-butyl-3-hydroxy-2-oxo-3-pyrroline-4-carboxylate (2·27 g., 0·01 mole) and benzaldehyde (1·17 g.,

0·011 mole). The product (1·1 g., 45%) had m.p. 133—134° (from ethanol) (Found: C, 74·1; H, 6·8; N, 5·7. $C_{15}H_{17}NO_2$ requires C, 74·1; H, 7·0; N, 5·8%).

1-*Butyl*-4-(2-*chlorobenzylidene*)*pyrrolidine*-2,3-*dione* (IIb).—This compound was prepared by the method described above using 2-chlorobenzaldehyde (1·54 g., 0·011 mole). The product (1·1 g., 40%) had m.p. 136—137° (from ethanol) (Found: C, 64·4; H, 5·9; N, 5·0. $C_{15}H_{16}ClNO_2$ requires C, 64·9; H, 5·8; N, 5·0%).

2-*Butyl*-4-*phenylpyrrolo*[c][1,5]*benzothiazepin*-1(2H)-*one* (IIIa).—4-Benzylidene-1-butylpyrrolidine-2,3-dione (2·43 g., 0·01 mole) and 2-aminobenzenethiol (1·25 g., 0·01 mole) were heated under reflux in ethanol (50 ml.) for 1 hr. The reaction mixture was cooled and the precipitated solid was collected and recrystallised, m.p. 163·5—164·5° (from ethanol) (Found: C, 72·1; H, 6·1; N, 8·0. $C_{21}H_{22}N_2OS$ requires C, 71·9; H, 6·3; N, 8·0%), $\nu_{max.}$ 3280, 1685, and 1580 cm.$^{-1}$; τ (100 MHz) 2·84 (10H, m), 3·06 (NH_2 exchangeable [6]), 5·02 (1H, s), 6·34 (2H, s), 6·54 (2H, t, J 7 Hz), 8·54 (4H, m), 9·03 (3H, t, J 7 Hz); yield 2·4 g. (68%).

2-*Butyl*-4-(2-*chlorophenyl*)*pyrrolo*[c][1,5]*benzothiazepin*-1(2H)-*one* (IIIb).—This compound was prepared by the method described above from 1-butyl-4-(2-chlorobenzylidene)pyrrolidine-2,3-dione (2·78 g., 0·01 mole). The product was recrystallised, m.p. 172—173° (from ethanol) (Found: C, 65·25; H, 6·5; N, 7·0. $C_{21}H_{21}ClN_2OS$ requires C, 65·5; H, 5·5; N, 7·3%), $\nu_{max.}$ 3280, 1685, and 1580 cm.$^{-1}$; τ 2·86 (9H, m), 4·59 (1H, s), 6·32 (2H, s), 6·47 (2H, t, J 7 Hz), 8·45 (4H, m), and 9·09 (3H, t, J 7 Hz).

2-*Butyl*-4-(2-*chlorophenyl*)*pyrrolo*[c][1,5]*benzothiazepin*-1(2H)-*one* SS-*Dioxide*.—A solution of 2-butyl-4-(2-chlorophenyl)pyrrolo[*c*][1,5]benzothiazepin-1(2*H*)-one (1·9 g., 5 mmole) in glacial acetic acid (50 ml.) containing hydrogen peroxide (1·5 g., 27%) was heated on a water-bath for 5 hr. The reaction mixture was poured onto ice–water (300 ml.). The solid which formed after several hours, was collected and recrystallised (1·4 g., 67%), m.p. 221—222° (from propanol) (Found: C, 60·6; H, 5·1; N, 6·45. $C_{21}H_{21}ClN_2O_3S$ requires C, 60·5; H, 5·1; N, 6·7%), $\nu_{max.}$ 3300, 1680, 1600, 1310, and 1140 cm.$^{-1}$.

4-(α-*Benzylthiobenzyl*)-1-*butyl*-3-*hydroxy*-3-*pyrrolin*-2-*one* (V).—4-Benzylidene-1-butylpyrrolidine-2,3-dione (2·4 g., 0·01 mole) and toluene-α-thiol (1·3 g., 0·01 mole) in ethanol (50 ml.) were treated with piperidine (0·2 mole). The mixture was heated under reflux for 0·25 hr. The solvent was distilled off and the solid which formed as the mixture cooled was collected and recrystallised (2·8 g., 76%), m.p. 135—136·5° (from ethanol) (Found: C, 72·2; H, 6·6; N, 3·7. $C_{22}H_{25}NO_2S$ requires C, 71·9; H, 6·9; N, 3·8%), $\nu_{max.}$ 3150 and 1675 cm.$^{-1}$.

1-*Butyl*-3-*hydroxy*-4-(α-*phenylthiobenzyl*-3-*pyrrolin*-2-*one* (IV).—This compound was prepared in a manner similar to that described above from 4-benzylidene-1-butylpyrrolidine-2,3-dione (2·4 g., 0·01 mole) and benzenethiol (1·1 g., 0·01 mole). The product was recrystallised (2·2 g., 62%), m.p. 120—121·5° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 71·6; H, 6·6; N, 4·1. $C_{21}H_{23}NO_2S$ requires C, 71·3; H, 6·6; N, 4·0%), $\nu_{max.}$ 3150 and 1675 cm.$^{-1}$.

Reaction of 4-(α-*Benzylthiobenzyl*)-1-*butyl*-3-*hydroxy*-3-*pyrrolin*-2-*one with* 2-*Aminobenzenethiol*.—The title compound (1·8 g., 5 mmole) and 2-aminobenzenethiol (0·62 g., 0·005 mole) were heated under reflux in ethanol (25 ml.) for 1 hr. The solid which formed as the mixture cooled was collected and recrystallised to give 1-butyl-4-phenylpyrrolo[*c*][1,5]benzothiazepin-1(2*H*)-one (1·35 g., 77%), m.p. and mixed m.p. 163—164°.

Reaction of 4-*Benzylidene*-1-*butylpyrrolidine*-2,3-*dione with Aromatic Amines*.—4-Benzylidene-1-butylpyrrolidine-2,3-dione (2·4 g., 0·01 mole) and redistilled aniline (2·8 g., 0·03 mole) in ethanol (50 ml.) were heated under reflux for 1 hr. The reaction mixture was evaporated to half volume under reduced pressure and stored over night at 0°. The 1-butyl-3-phenylamino-3-pyrrolin-2-one which separated was recrystallised (0·31 g., 13%) (from ethanol), m.p. and mixed m.p. 150—151°. The filtrate from the reaction mixture was evaporated under reduced pressure leaving a semisolid which was washed with ice-cold ethanol. 3-Anilino-4-(α-anilinobenzyl)-1-butyl-3-pyrrolin-2-one (0·38 g., 9%) was obtained as prisms, m.p. 138—140° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 78·5; H, 7·15; N, 10·2. $C_{27}H_{29}N_3O$ requires C, 78·8; H, 7·1; N, 10·2%), $\nu_{max.}$ 3400, 3275, 1695, and 1665 cm.$^{-1}$; τ 3·00 (15H, m), 3·94 (1H, s, exchangeable), 3·62 (1H, s), 4·70 (1H, s), 6·20 (2H, s), 6·60 (2H, t, J 7 Hz), 8·64 (4H, m), 9·12 (3H, t, J 7 Hz).

The filtrate from the second reaction product was evaporated to a dark oil which did not crystallise. Heating this residue with 2N-hydrochloric acid (10 ml.) for 0·5 hr. and then treating the reaction mixture with an ethanolic solution of Brady's Reagent gave an orange solid, m.p. 237—240°. Admixture with benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 237—240°.

4-*Aminothioanisole*.—In this series of experiments, using the method described above, aniline was replaced by 4-methylthioaniline.

1-*Butyl*-3-(4-*methylthioanilino*)-4-[α-(4-*methylthioanilino*)-*benzyl*]-3-*pyrrolin*-2-*one* (VIb). The crystallised product (0·3 g., 7%) had m.p. 140—142° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 69·2; H, 6·5; N, 8·6. $C_{29}H_{33}N_3OS$ requires C, 69·1; H, 6·6; N, 8·3%), $\nu_{max.}$ 3400, 3260, 1670, and 1610 cm.$^{-1}$.

1-*Butyl*-3-(4-*methylthioanilino*)-3-*pyrrolin*-2-*one* (VIIb). The crystallised product (0·38 g., 14%) had m.p. 139—141° (from ethanol) (Found: C, 65·5; H, 7·15; N, 10·3. $C_{15}H_{20}N_2OS$ requires C, 65·1; H, 7·3; N, 10·1%).

N-*Benzylidene*-4-*methylthioaniline* (VIII).—The crystallised product (0·29 g., 13%) had m.p. 75—78° [from benzene-light petroleum (b.p. 60—80°)] (Found: C, 74·0; H, 5·8; N, 6·0. $C_{14}H_{13}NS$ requires C, 74·0; H, 5·8; N, 6·2%).

Reaction of 1-*Butyl*-3-*hydroxy*-4-(α-*phenylthiobenzyl*)-3-*pyrrolin*-2-*one* (IV) *with Aniline*.—The title compound (1·81 g., 0·005 mole) and aniline (2·4 g., 0·026 mole) in ethanol (50 ml.) were heated under reflux for 2·5 hr. The solvent was evaporated to leave the pyrolinone (IV) (0·56 g., 27%) [from benzene–light petroleum (b.p. 60—80°)] m.p. and mixed m.p. 138—140°.

3-*Anilino*-1-*butyl*-4-(α-*phenylthiobenzyl*)-3-*pyrrolin*-2-*one* (IX).—The pyrrolinone (IIa) (2·05 g., 0·005 mole), benzenethiol (2·7 g., 0·025 mole), and piperidine (0·2 ml.) in ethanol (50 ml.) were heated under reflux for 1 hr. Evaporation of the solvent gave the *pyrrolinone* (IX) (0·45 g., 21%), m.p. 111—113° (from ethanol) (Found: C, 76·0; H, 6·8; N, 6·5. $C_{27}H_{28}N_2OS$ requires C, 75·7; H, 6·6; N, 6·5%), $\nu_{max.}$ 3270, 1680, and 1600 cm.$^{-1}$.

Amination of 1-*Butyl*-3-*hydroxy*-4-(α-*phenylthiobenzyl*)-3-*pyrrolin*-2-*one* (IV).—The title compound (1·81 g., 0·005

mole), formic acid (0·92 g., 0·02 mole), and aniline (1·86 g., 0·02 mole) in ethanol (50 ml.) were heated under reflux for 6 hr. The pyrrolinone (IV) crystallised from the cool mixture (1·1 g., 51%), m.p. and mixed m.p. 111—113° (from ethanol).

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