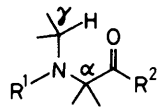
Photoreactions of α-Amino Ketones Derived from Heterocyclic Secondary Amines

John Hill,* Marwan M. Zakaria, and (in part) David Mumford
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

The photochemical behaviour of *N*-phenacyl nitrogen heterocycles varies with the size of the heterocyclic ring. U.v. irradiation of 1-phenacylindoline and 2,3,3-trimethyl-1-phenacylindoline resulted in type-II fission to give acetophenone and indole or 2,3,3-trimethyl-3*H*-indole, respectively. Indole was also produced, along with 2,3-diphenylbutane-2,3-diol, when indoline was irradiated with acetophenone. Both 1-phenacyl- and 1-(2-oxocyclohexyl)-1,2,3,4-tetrahydroquinoline underwent type-II cyclisation to azetidinol derivatives; fission was a minor process. In contrast, on irradiation of 5,6-dihydro-5-phenacylphenanthridine, type-II fission occurred to give acetophenone and phenanthridine. Irradiation of 2,3,4,5-tetrahydro-1-phenacyl-1*H*-benz[*b*]azepine resulted in direct homolysis of the N–CH_2CO bond to yield 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine as the major product.

The photochemistry of an α-amino ketone (1) is highly dependent on its structure, particularly on the nature of groups R^1 and R^2. Intramolecular transfer of hydrogen from the γ-carbon to oxygen (type-II photoreaction) followed by fission (to an enol and an imine) or cyclisation to an azetidinol, or direct homolysis of the N–C_α bond to give radicals are the more typical photoreactions.[1] The following results show that when the nitrogen atom of an amino ketone (1) is part of a heterocyclic ring, as in (2), the size of the ring is an important factor regarding the photochemistry of the amino ketone.



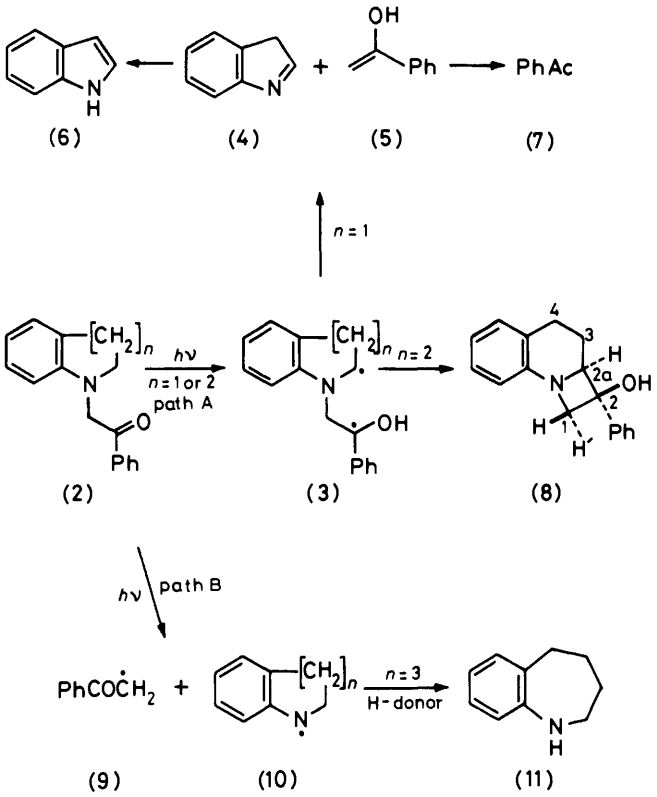
(1)

5-Membered Ring Heterocyclic Amino Ketones.—Irradiation of a solution of 1-phenacylindoline (2a) in diethyl ether yielded indole (6) (68%) and acetophenone (7) (17%). The two more likely reaction pathways are (i) type-II fission (path A, Scheme) to 3*H*-indole (4) and the enol (5) followed by tautomerisation to the more stable indole (6) and acetophenone (7) respectively, and (ii) direct homolysis (path B) to radicals (9) and (10a) followed by hydrogen abstraction to give acetophenone and indoline (12) which then undergoes photodehydrogenation to indole (6). To test the feasibility of pathway (ii), indoline (12) was irradiated in the presence of acetophenone with diethyl ether as the solvent. A 34% conversion of indoline into indole took place with a simultaneous reduction of acetophenone to the pinacol (13), and indoline (42%) was recovered. The absence of significant amounts of pinacol (13) and indoline (12) amongst the photoproducts from the amino ketone (2a) provides strong evidence against the proposed reaction pathway (ii). Pathway (i) [type-II photoreaction (path A) followed by disproportionation (fission)] leads first to 3*H*-indole (4) and the enol (5) as unstable intermediates. Evidence supporting the formation of a 3*H*-indole intermediate was provided by irradiating 2,3,3-trimethyl-1-phenacylindoline (14). The products were acetophenone and the stable 2,3,3-trimethyl-3*H*-indole (15) which was formed in almost quantitative yield. Thus, the major photoreaction of 1-phenacylindolines appears to be type-II fission. Cyclisation of the intermediate biradical (3a) to an azetidinol derivative presumably does not occur as the transition state for cyclisation would have a relatively high degree of angle strain [compared with that for cyclisation to the azetidinol (8)]. Type-II cyclisation to an azetidinol is the preferred photoreaction of the structurally related amino ketones (16) in which the nitrogen atom is not part of a ring.[2]

6-Membered Ring Heterocyclic Amino Ketones.—When 1,2,3,4-tetrahydro-1-phenacylquinoline (2b) was irradiated with diethyl ether as the solvent, the major product (27%) was the azetidinol derivative (8). A little (4%) acetophenone (7), a type-II fission product, was also produced. In this case the predominant photoreaction is type-II cyclisation. Unlike the biradical (3a) formed from amino ketone (2a), the intermediate biradical (3b) cyclises readily and cleavage is a minor process. As 2-(*N*-alkylarylamino)cyclohexanones also undergo type-II cyclisation to azetidinols,[1] the aminocyclohexanone (17) was irradiated as a solution in tetrahydrofuran (THF). Again, the major product (20%) was an azetidinol derivative [*i.e.* (18)].

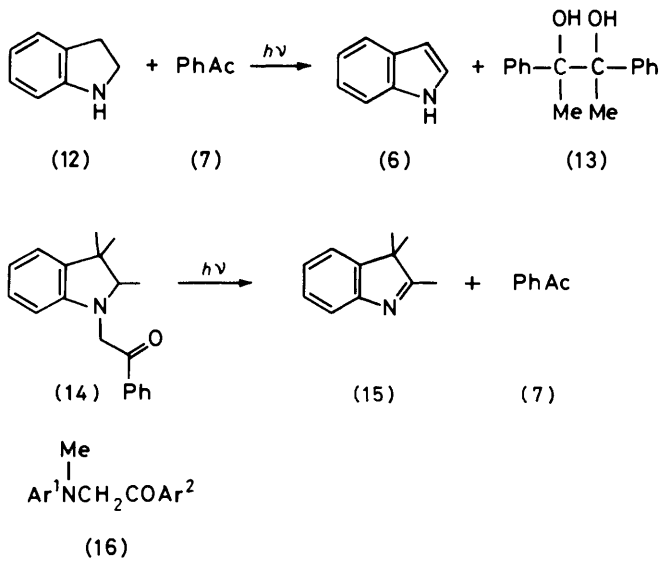
The structures of the azetidinols (8) and (18) were consistent with their i.r., n.m.r., and mass spectra. The more abundant ions in the mass spectra result from cleavage of the azetidine ring in a manner which has been described previously for other azetidinols.[3] Assignment of stereochemistry for 2,2a,3,4-tetrahydro-2-phenyl-1*H*-azeto[1,2-*a*]quinolin-2-ol (8), in which the OH group and 2a-H are *trans*, is based on europium-induced increases in chemical shifts, in the n.m.r. spectrum, of the OH, 1-H′, and 1- and 2a-H protons of 100, 12, 19, and 13% respectively (figures denote percentages of the OH shift; see also the Experimental section). The stereochemistry of the azetidinol (18) was not investigated. By analogy with the structure of the azetidinol formed on irradiation of 2-(*N*-methylanilino)cyclohexanone,[1] a *cis* ring junction between the cyclohexane and azetidine rings would be expected.

To investigate a system in which disproportionation (fission) of a biradical of type (3b) would be more competitive with cyclisation, 5,6-dihydro-5-phenacylphenanthridine (19) was irradiated with THF as the solvent. Here, cleavage in the intermediate type-II biradical (20) is favoured by concurrent aromatisation to the product phenanthridine (21), which was formed in good yield (70%) along with the other cleavage product acetophenone (7). 5,6-Dihydrophenanthridine (22), which could be oxidised to phenanthridine during work-up, was shown (t.l.c.) not to be present in the photolysis mixture. It therefore appears that type-II cyclisation to azetidinols is the preferred photoreaction of *N*-(2-oxoalkyl)tetrahydroquinolines [(2b) and (17)] except in cases where cleavage involves aromatisation. It may also be more difficult for the



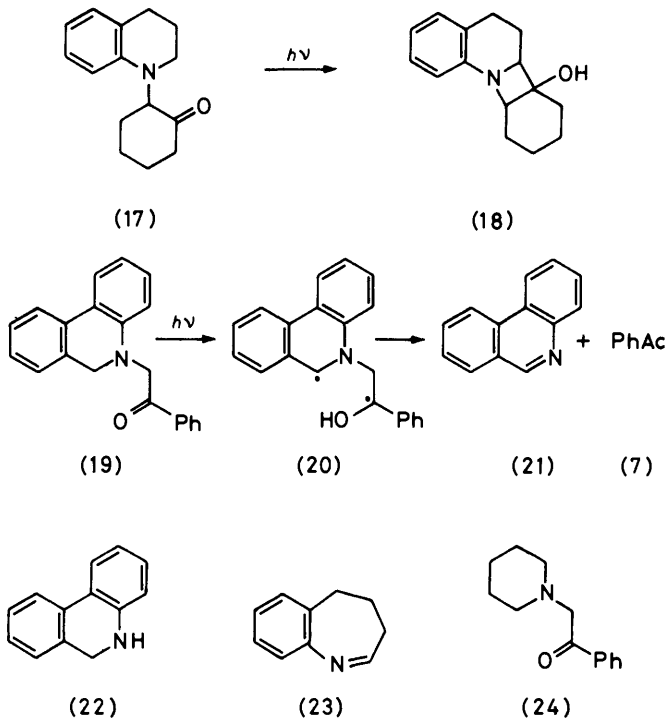
(2), (3), and (10) a; $n = 1$
b; $n = 2$
c; $n = 3$

Scheme.



more planar biradical (20) to achieve a suitable conformation for cyclisation than is the case for the less planar biradical (3b).

A 7-Membered Ring Heterocyclic Amino Ketone.—When a solution of 2,3,4,5-tetrahydro-1-phenacyl-1*H*-benz[*b*]azepine (2c) in diethyl ether was irradiated, a complex mixture containing tetrahydrobenz[*b*]azepine (11) (33%) was produced. The formation of a secondary amine and the absence of a



significant amount of the type-II fission product (7) suggests that the major photoreaction is direct homolysis to radicals (9) and (10c) (path B, Scheme).* None of the other type-II fission product (23), or products derived from it, could be detected. The reluctance of the amino ketone (2c) to undergo a type-II photoreaction is probably due to the non-bonded repulsive interactions involving the azepine ring hydrogens in the transition state for intramolecular hydrogen abstraction. Such interactions are less important in the case of amino ketones (2a) and (2b).

1-*Phenacylpiperidine* (24).[4]—In each of the above amino ketones the nitrogen atom is conjugated to a benzene ring and the resulting delocalisation of the nitrogen lone-pair electrons appears to be important regarding amino ketone photochemistry.[1] Irradiation of a solution of the 6-membered ring heterocyclic amino ketone (24), in which the lone-pair is localised on nitrogen, gave a complex mixture. No product was isolated and no type-II product could be detected in the photolysis mixture.

Experimental

All irradiations were carried out on stirred solutions under nitrogen with the light source (a high-pressure mercury vapour lamp obtained by removing the outer glass envelope from a 125-W Thorn Electric Kolorlux MBF bulb) centrally situated in a water-cooled Pyrex cold finger, unless otherwise stated. Silica gel used for column chromatography was Hopkin and Williams M.F.C. Light petroleum had b.p. 60—80 °C. I.r. spectra were recorded as Nujol mulls (for solids) or liquid films, and ^{1}H n.m.r. spectra (data in δ values) were recorded in $CDCl_3$ with $SiMe_4$ as internal standard.

Preparation of Amino Ketones (2a—c), (14), *and* (19).—A solution of phenacyl bromide (1 equiv.) in ethanol was heated

* See references 1 and 2 for a discussion of the fate of imines [*cf.* (23)] formed by type-II fission and the mechanism of secondary amine formation.

under reflux with the appropriate secondary amine (1.1 equiv.) in the presence of anhydrous sodium carbonate (1 equiv.). The reaction was carried out under an atmosphere of nitrogen in the preparation of (19) only. A little water (up to 20% of the volume of ethanol) was added and the mixture was cooled and filtered. The crude solid product was extracted into chloroform. Evaporation of the extract followed by crystallisation of the residue gave the amino ketone. Reaction time and yield are given below.

1-*Phenacylindoline* (2a), 1 h (95%), m.p. 110—111 °C (from ethanol) (Found: C, 81.1; H, 6.5; N, 6.0. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.4; N, 5.9%); $\nu_{max.}$ 1 690 cm^{-1}; δ 2.8—3.8 (4 H, A_2B_2 m centred at 3.28, 2 × CH_2), 4.51 (s, NCH_2CO), and 6.35—8.25 (9 H, m, ArH); *m/z* 237 (M^+, 13%), 132(100), 130(17), 117(23), 103(10), and 77(32). 1,2,3,4-*Tetrahydro*-1-*phenacylquinoline* (2b), 1 h (82%), m.p. 99—101 °C (from ethanol) (Found: C, 80.95; H, 6.9; N, 5.4. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6%); $\nu_{max.}$ 1 690 cm^{-1}; δ(CCl_4) 1.65—2.15 (m, CH_2), 2.55—2.85 (m, $ArCH_2$), 3.1—3.4 (m, NCH_2), 4.47 (s, NCH_2CO), and 6.05—8.05 (9 H, m, ArH); *m/z* 251 (M^+, 8%), 146(100), 131(10), 130(10), 118(17), 117(10), 91(23), and 77(14). 2,3,4,5-*Tetrahydro*-1-*phenacyl*-1H-*benz*[b]*azepine* (2c), 24 h (90%), m.p. 69—70 °C (from methanol) (Found: C, 81.4; H, 7.5; N, 5.3. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%); $\nu_{max.}$ 1 690 cm^{-1}; δ 1.4—1.8 (m, 2 × CH_2), 2.6—2.9 (m, $ArCH_2$), 2.9—3.2 (m, NCH_2), 4.58 (s, NCH_2CO), and 6.75—8.05 (9 H, m, ArH); *m/z* 265 (M^+, 0.2%), 160(10), 146(9), 130(17), 118(100), 106(14), 91(40), and 77(24). 2,3,3-*Trimethyl*-1-*phenacylindoline* (14), 1.5 h (93%), m.p. 96—97 °C (from light petroleum) (Found: C, 81.5; H, 7.8; N, 4.9. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%); $\nu_{max.}$ 1 680 cm^{-1}; δ 1.03 (s, Me), 1.11 (d, *J* 7 Hz, CH*Me*), 1.28 (s, Me), 3.46 (q, *J* 7 Hz, C*H*Me), 4.47 (s, NCH_2CO), and 6.25—8.1 (9 H, m, ArH); *m/z* 279 (M^+, 19%), 174(100), 158(12), 144(22), 132(15), 118(15), 91(11), and 77(16). 5,6-*Dihydro*-5-*phenacylphenanthridine* (19), 2 h (75%), m.p. 126—129 °C (from ethanol–toluene) (Found: C, 84.2; H, 5.7; N, 4.8. $C_{21}H_{17}NO$ requires C, 84.3; H, 5.7; N, 4.7%); $\nu_{max.}$ 1 680 cm^{-1}; δ 4.3 (s, NCH_2), 4.5 (s, $COCH_2$), and 5.9—7.8 (13 H, m, ArH); *m/z* 299 (M^+, 16%), 195(66), 179(92), 166(100), 165(88), 152(22), and 105(26).

1,2,3,4-*Tetrahydro*-1-(2-*oxocyclohexyl*)*quinoline* (17).—2-Chlorocyclohexanone (2 g), 1,2,3,4-tetrahydroquinoline (2.1 g), quinoline (0.2 g), anhydrous sodium carbonate (4 g), and 2-methoxyethanol (15 ml) were heated under reflux for 1 h.[5] The mixture was cooled and filtered, and the solids were washed with methanol. After evaporation of the filtrate the residue was treated with a solution of picric acid in benzene and the resulting insoluble tetrahydroquinoline picrate was filtered off. Diethyl ether was added to the filtrate and the ethereal solution was washed in turn with aqueous sodium hydrogen carbonate and water. Evaporation of the dried organic solution yielded the crude amino ketone (17) (1.7 g), $\nu_{max.}$ 1 720 cm^{-1}; δ 1.1—2.5 (m, 5 × CH_2), 2.5—2.9 (m, $ArCH_2$), 3.2—3.5 (m, NCH_2), 4.0—4.45 (m, NCHCO), and 6.1—7.4 (4 H, m, ArH).

Treatment of the crude amino ketone with a solution of 2,4-dinitrophenylhydrazine in dimethyl sulphoxide containing a little acetic acid gave the 2,4-*dinitrophenylhydrazone*, m.p. 102—103 °C (from ethanol) (Found: C, 61.6; H, 5.4; N, 17.1. $C_{21}H_{23}N_5O_4$ requires C, 61.6; H, 5.7; N, 17.1%).

Apart from commercially available materials, the following were prepared according to literature methods; 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine (11),[6] 2,3,3-trimethylindoline,[7] and 1-phenacylpiperidine (24).[4] After reduction of phenanthridine to 5,6-dihydrophenanthridine (22) in Sn–HCl,[8] basification was carried out with aqueous sodium hydroxide containing sodium dithionite, and work-up was rapid to avoid oxidation of the product.

Irradiation of 1-*Phenacylindoline* (2a).—A 0.9% solution of the amino ketone (2a) in diethyl ether was irradiated for 5.25 h. After evaporation of the solvent the residue was chromatographed over silica gel. Elution with toluene–light petroleum (1 : 1) yielded indole (6) (68%) and elution with 1% ethyl acetate in toluene gave acetophenone (7) isolated as its 2,4-dinitrophenylhydrazone (17%).

Irradiation of 2,3,3-*Trimethyl*-1-*phenacylindoline* (14).—A 1% solution of the amino ketone (14) in diethyl ether was irradiated for 2.75 h. Extraction into 2M hydrochloric acid, followed by basification, yielded 2,3,3-trimethyl-3*H*-indole (15) (*ca.* 100%). Treatment of the non-basic photolysate with acidified 2,4-dinitrophenylhydrazine in ethanol gave acetophenone 2,4-dinitrophenylhydrazone (39%).

Irradiation of Indoline (12) *with Acetophenone* (7).—A solution of indoline (12) (2.4 g) and acetophenone (7) (2.4 g) in diethyl ether (125 ml) was irradiated for 5 h. Extraction of the product with 2M hydrochloric acid, followed by basification, yielded crude indoline which, on extraction into light petroleum and evaporation of the extract, gave recovered indoline (1 g). The non-basic photolysate was chromatographed over silica gel. Elution with toluene–light petroleum (1 : 1) gave indole (6) (0.81 g) and elution with 2% methanol in toluene gave 2,3-diphenylbutane-2,3-diol (13) (2.08 g), m.p. 119—120 °C (from aqueous ethanol).

Irradiation of 1,2,3,4-*Tetrahydro*-1-*phenacylquinoline* (2b).—A 1.5% solution of the amino ketone (2b) in diethyl ether was irradiated for 4.75 h. The ether was evaporated off and the residue was chromatographed over silica gel. Elution with 1% ethyl acetate in toluene yielded acetophenone (7) isolated as its 2,4-dinitrophenylhydrazone (4%) and elution with 2—4% ethyl acetate in toluene gave 2,2a,3,4-*tetrahydro*-2-*phenyl*-1H-*azeto*[1,2-a]*quinolin*-2-*ol* (8) (27%), m.p. 108—109 °C (from light petroleum) (Found: C, 81.4; H, 6.9; N, 5.5. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6%); $\nu_{max.}$ 3 420br cm^{-1}; δ 1.67—2.0 (m, 3-H_2), *ca.* 2.6 (OH), 2.3—2.9 (m, $ArCH_2$), 3.76 (d, *J* 9 Hz, 1-H), 4.27 (dd, both *J ca.* 8 Hz, 2a-H), 4.42 (d, *J* 9 Hz, 1-H′), and 6.4—7.7 (9 H, m, ArH); δ [$CDCl_3$ + Eu(fod)$_3$*] *ca.* 2.0—2.8 (m, 3-H_2), *ca.* 2.6—3.0 (m, $ArCH_2$), 4.36 (d, *J* 9 Hz, 1-H), 4.68 (dd, *J ca.* 6 and *ca.* 10 Hz, 2a-H), 4.8 (d, *J* 9 Hz, 1-H′), 5.84 (br s, OH), and 6.55—8.2 (9 H, m, ArH); *m/z* 251 (M^+, 3%), 132(100), 131(18), 130(38), 118(15), 117(15), 105(18), 91(15), and 77(33).

Irradiation of 1,2,3,4-*Tetrahydro*-1-(2-*oxocyclohexyl*)*quinoline* (17).—A solution of the amino ketone (17) in THF was irradiated for 24 h using a 75-W high-pressure mercury vapour lamp (type Q81 Quarzlampen GMBH Hanau). Evaporation of the solvent and elution of the residue over silica gel with 5% ethyl acetate in toluene gave, first, the amino ketone (17) (70% recovery) and then 6,6a,6b,7,8,9,-10,10a-*octahydro*-5H-*benz*[3,4]*azeto*[1,2-a]*quinolin*-6b-*ol* (18) (20%), m.p. 104—105 °C (from light petroleum) (Found: C, 78.1; H, 8.3; N, 5.8. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.4; N, 6.1%); $\nu_{max.}$ 3 420br cm^{-1}; δ 1.51 (s, OH), 1.2—2.1 (m, 5 × CH_2), 2.4—2.75 (m, $ArCH_2$), 3.4—3.7 (m, 2 × NCH),

* Eu(fod)$_3$ = Europium tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate).

and 6.3—6.9 (4 H, m, ArH); *m/z* 229 (M^+, 12%), 133(15), 132(100), 130(20), 118(9), 117(9), 98(8), and 77(8).

Irradiation of 2,3,4,5-*Tetrahydro*-1-*phenacyl*-1H-*benz*-[b]-*azepine* (2c).—A 0.4% solution of the amino ketone (2c) in diethyl ether was irradiated for 8.5 h. The mixture was filtered and the filtrate was extracted into 2M hydrochloric acid. Basification yielded a crude product which, after extraction into light petroleum and evaporation of the solvent, gave 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine (11) (33%). The neutral photolysis mixture appeared to contain a trace of acetophenone (7) (t.l.c. examination).

Irradiation of 5,6-*Dihydro*-5-*phenacylphenanthridine* (19).—A 1% solution of the amino ketone (19) in THF was irradiated in a Rayonet RPR 100 photoreactor fitted with 3 000-Å lamps for 1.5 h. Extraction of the product with 2M hydrochloric acid followed by basification gave phenanthridine (21) (70%). Treatment of the neutral photolysate with acidified 2,4-dinitrophenylhydrazine in ethanol yielded acetophenone 2,4-dinitrophenylhydrazone (43%).

The known heterocycles indole (6), 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine (11),[6] 2,3,3-trimethyl-3*H*-indole (15),[9] and phenanthridine (21),[10] and 2,3-diphenylbutane-2,3-diol (13) [11] were identified by comparison (i.r. spectra) with authentic samples.

References

1 See A. A. El-Hamamy, J. Hill, and J. Townend, *J. Chem. Soc., Perkin Trans. 1*, 1983, 573 and references 2—10 therein.
2 K. L. Allworth, A. A. El-Hamamy, M. M. Hesabi, and J. Hill, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1671.
3 J. Clark and J. Hill, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1514.
4 H. Moehrle, *Arch. Pharm.* (*Weinheim, Ger.*), 1965, **298**, 658 (*Chem. Abstr.*, 1966, **64**, 3453).
5 General procedure of E. Campaigne and R. D. Lake, *J. Org. Chem.*, 1959, **24**, 478.
6 B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, 1955, **77**, 4079.
7 G. Plancher and D. Bettinelli, *Gazz. Chim. Ital.*, 1899, **29**, 106.
8 E. Ritchie, *J. Proc. R. Soc. N. S. Wales*, 1945, **78**, 177 (*Chem. Abstr.*, 1946, **40**, 881).
9 G. Plancher, *Ber.*, 1898, **31**, 1488.
10 E. C. Taylor, Jr. and N. W. Kalenda, *J. Am. Chem. Soc.*, 1954, **76**, 1699.
11 G. Ciamician and P. Silber, *Ber.*, 1900, **33**, 2911.

Received 26th January 1983; *Paper* 3/110