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HETEROCYCLIC COMPOUNDS-VI[1]

SOME PHENANTHRIDINE DERIVATIVES *VIA* ENAMINES

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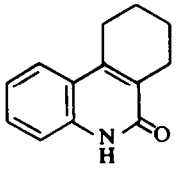
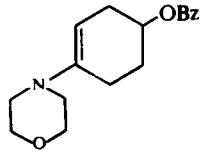
Abstract—Substituted tetrahydrophenanthridones obtained by the reaction of aryl isocyanates with enamines from 4-benzoyloxycyclohexanone have been transformed into a series of phenanthridine and tetrahydrophenanthridine derivatives possessing various functional groups.

PREVIOUSLY[1] we reported the preparation of tetrahydrophenanthridones of type **1** by the method of Ried and Kaeppeler.[2] We describe here an extension of this method for the synthesis of various phenanthridine derivatives in connection with a program on potential antimalarial compounds.

With the intention of introducing a functional group in **1**, the morpholine enamine from 4-benzoyloxycyclohexanone **2** was allowed to react with an aryl isocyanate. The enamide **3** thus formed in high yield was cyclized to the phenanthridone **4** in 80–90% yield by 70% sulfuric acid.



1



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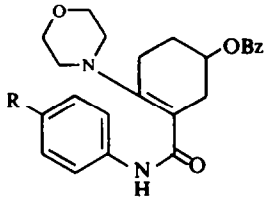
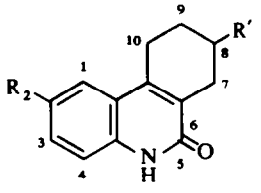


3a: R = OMe
3b: R = Me

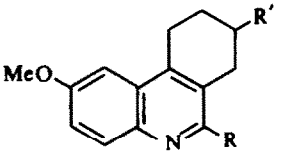


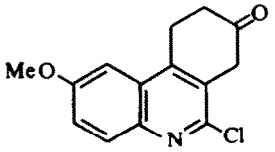
4a: R = OMe, R′ = OBz
4b: R = Me, R′ = OBz
4c: R = OMe, R′ = OH
4d: R = OMe, R′ = N

Hydrolysis of **4a** to **4c** was achieved in 60% yield by refluxing with alcoholic KOH aq. The oxidation of **4c** to ketone **8a** could not be accomplished using Jones

reagent or Sarett reagent-only water soluble materials were obtained. The use of a milder reagent, a sulfur trioxide–pyridine complex[4] in DMSO, led to ketone **8a** in satisfactory yield.

Treatment of **4a** with $POCl_3$ gave chloro compound **5a** which was easier to handle than **4a**. Hydrolysis of **5a** to alcohol **5b** proceeded in nearly quantitative yield. The oxidation of **5b** to ketone **6** could be performed smoothly with Jones reagent.





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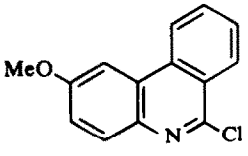
5a: R = Cl, R′ = OBz
5b: R = Cl, R′ = OH
5c: R = Cl, R′ = OTs
5d: R = H, R′ = OH
5e: R = H, R′ = OTs
5f: R = H, R′ = Cl

5g: R = Cl, R′ = 

We wished to introduce a double bond in the tetrahydrophenanthridine system that could be transformed by known reactions to an α-aminoalcohol function. With this aim **5b** was reduced to **5d** by catalytic hydrogenation and its tosyl derivative **5e** was heated with LiCl in DMF. The only product isolated was the 8-chlorotetrahydrophenanthridine **5f**. In an alternative approach, tosyl derivative **5c** was treated with t-BuOk in DMF at room temperature under N_2. The reaction product was identified as 6-chloro-2-methoxyphenanthridine **7**. Apparently, once a double bond was introduced by an elimination reaction, oxidation to the fully aromatic state **7** proceeded very readily.



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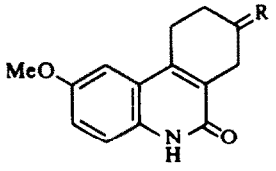
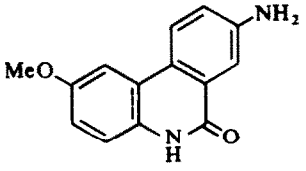


8a: R = O
8b: R = NOH



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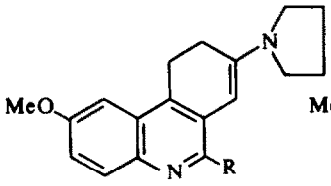
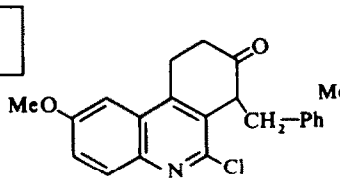
The ease with which phenanthridine derivatives such as **5c**, undergo aromatization was also demonstrated by **8a**. Oxime **8b** from **8a** was subjected to conditions for Beckmann rearrangement (heating with polyphosphoric acid), a product was obtained in excellent yield to which the structure **9** has been assigned on the basis of spectral data. Obviously, Semmler–Wolff type of rearrangement[5, 6] had occurred in preference to the Beckmann rearrangement. The aromatic amino group of **9** and its analogs could serve as functionality for introducing various groups at position-8 by standard reactions.

The enamines **10a** and **10b** could be readily obtained by refluxing **8a** and **6**, respectively with pyrrolidine. The alkylation of **10b** with benzyl chloride proceeded smoothly to give **11**.



10a: R = OH*
10b: R = Cl



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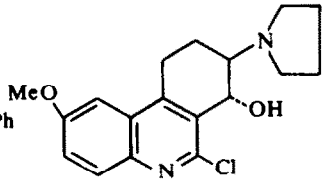

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The reaction of an enamine with diborane has been reported to give a number of different products. Marshall and Johnson[7] prepared β, γ-unsaturated amines by reduction of a steroid dienamine with $NaBH_4$ followed by cleavage of the aminoborane intermediate with AcOH. Under similar conditions Lewis and Pearce[8] obtained alkenes using enamines derived from saturated cyclic and acyclic ketones. Borowitz and Williams[9] reported that the aminoboranes can be oxidized with alkaline H_2O_2 to the β-amino-carbinols**. However, when **10b** was treated with boron trifluoride etherate and LAH followed by alkaline H_2O_2, no evidence was found for the formation of expected **12**,[8] instead **5b** was obtained. It would appear that enamine **10b** had reverted to the parent ketone **6** which had undergone reduction to produce the hydroxy compound **5b**. As suggested by a referee, **5b** could also arise through initial formation of the olefin[8] which then underwent hydroboration and hydrogen peroxide oxidation. Another product of this reaction which appeared to be **5g** on the basis of spectroscopic data was not studied further.

Attempts to reduce the enamine **10b** with $NaBH_4$ in MeOH followed by AcOH were unsuccessful and in each case intractable material was obtained. However, **10a** under similar conditions afforded amine **4d** in 40% yield. Thus, reaction of enamine **10a**, which is a part of a conjugated system, is similar to that of the dienamines reported by Marshall and Johnson[7]. Formation of by product **5g** from **10b** is also consistent with this view. Obviously, the course of the reaction of enamines with diborane or equivalent is particularly sensitive to reaction conditions.

EXPERIMENTAL

IR spectra were recorded in nujol on a Perkin–Elmer Infracord Spectrophotometer. PMR spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz using TMS as internal standard. The mass spectra were recorded on a CEC-103C mass spectrometer at 70 e.v. using an all glass heated inlet system.

4-Benzoyloxy-1-morpholinocyclohexene (**2**). A solution of 4-benzoyloxycyclohexanone[3] (150 g; 0·691 mole) in 300 ml benzene containing 62 g (0·713 mole) morpholine and 1 g of *p*-TsOH was heated at reflux overnight in a Dean-Stark apparatus. Removal of solvent afforded 179 g of enamine (90%), m.p. 130° (ether–benzene). ν_{max} 1725, 1660 cm^{-1}, NMR ($CDCl_3$) τ: 1·9 (m, 2H); 2·5 (m, 3H); 4·7 (m, 1H); 5·4 (t, 1H); 6·25 (t, 4H); 7·2 (t, 4H); 7·8 (m, 6H). (Found: C, 71·03; H, 7·36; N, 4·63. $C_{17}H_{21}NO_3$ requires: C, 71·05; H, 7·37; N, 4·87%).

5-Benzoyloxy-N(p-methoxyphenyl)-2-morpholino-2-cyclohexenecarboxamide (**3a**). To a solution of 14·9 g (0·1 mole) of p-methoxyphenylisocyanate in 50 ml $CHCl_3$ was added dropwise a solution of 28·7 g

* Compound 10a exists in the amide form.
** This reaction was previously reported by G. Stork, see footnote Ref. 8.

(0·1 mole) of 4-benzoyloxycyclohexenylmorpholine (**2**) in 100 ml $CHCl_3$. After addition, the contents were stirred for 15 min. and then heated at reflux for 10 min. Solvent was removed under vacuum and the product purified by washing (dry ether and small amounts of MeOH) to give 33 g (77·5%) of the product, m.p. 156–157° (C_6H_6—CH_2Cl_2). ν_{max} 1724, 1667, 1613 cm^{-1} NMR ($CDCl_3$) τ: 1·9–3·2 (m, 10H); 4·85 (m, 1H); 6·25 (m, 7H), 6·9–8·1 (m, 10H). (Found: C, 68·90; H, 6·39; N, 6·27. $C_{25}H_{28}N_2O_5$ requires: C, 68·79; H, 6·47; N, 6·42%).

*5-Benzoyloxy-2-morpholino-*N(p-*tolyl*)*-2-cyclohexene-carboxamide* (**3b**). This compound was prepared in 85% yield from *p*-tolylisocyanate and 4-benzoyloxy-morpholino cyclohexene as described under **3a**, m.p. 156–157° ($CHCl_3$-ether).

8-Benzoyloxy-2-methoxy-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine (**4a**). N-(*p*-Methoxyphenyl)-2-morpholino-5-benzoyloxy-2-cyclohexene-carboxamide (135 g) was dissolved in 1350 ml of 70% H_2SO_4 and kept at room temperature for two days. The mixture was poured into excess ice to give a white precipitate. The solid was washed successively with ether and MeOH to give 55 g (50%) of product, m.p. 265°. ν_{max} 1724, 1667 cm^{-1} NMR (DMSO-d_6) τ: 2·05 (m, 2H); 2·25—2·9 (m, 7H); 4·55 (m, 1H); 6·15 (s, 3H); 7·8 (m, 6H). Mass spectrum, M^+ at *m/e* 349. (Found: C, 72·45; H, 5·57; N, 3·81. $C_{21}H_{19}NO_4$ requires: C; 72·19; H, 5·48; N, 4·01%).

8-Benzoyloxy-2-methyl-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine (**4b**). Cyclization of the enamide **3b** with 70% H_2SO_4 provided the title compound in 70% yield, m.p. 291–92° (DMF). (Found: C, 75·43; H, 5·91; N, 4·02: $C_{21}H_{19}NO_3$ requires: C, 75·65; H, 5·75; N, 4·20%).

8-Hydroxy-2-methoxy-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine (**4c**). To a solution of 5 g of the benzoate in 20 ml of dioxane was added 50 ml of 10% KOH aq and the contents refluxed for 40 min. The mixture was then decomposed by excess ice and the white solid crystallized from DMF to give 3·2 g (100%) of product, m.p. 255°; ν_{max} 3510, 1667 cm^{-1}, Mass spectrum, M^+ at *m/e* 245. (Found: C, 68·48; H, 6·15; N, 5·72. $C_{14}H_{15}NO_3$ requires: C, 68·55; H, 6·16; N, 5·71%).

2-Methoxy-6-oxo-8-pyrrolidino-5,6,7,8,9,10-hexahydrophenanthridine (**4d**). To a solution of 0·5 g (0·00169 mole) of enamine **10a**, obtained by refluxing ketone **8a** with pyrrolidine, in 10 ml of dioxane was added a solution of 0·2 g (0·0053 mole) of $NaBH_4$ in 7 ml of MeOH. The contents were stirred at room temperature for 2 hr and warmed with 15 ml AcOH for a few min. Sufficient water was added and the solution made alkaline with $NaHCO_3$. Extraction with $CHCl_3$ and solvent evaporation provided **4d**, m.p. 240–245 (MeOH–C_6H_6), yield 40%. ν_{max} 1667 cm^{-1}; Mass spectrum, M^+ at *m/e*, 298; (Found: C, 72·47; H, 7·51; N, 9·19. $C_{18}H_{22}N_2O_2$ requires: C, 72·45; H, 7·43; N, 9·39%).

8-Benzoyloxy-6-chloro-2-methoxy-7,8,9,10-tetrahydrophenanthridine (**5a**). 8-Benzoyloxy-2-methoxy-6-oxo-5,6,7,8,9,10-hexahydrophenanthridine (**4a**) (15 g, 0·043 mole) was treated with $POCl_3$ (60 ml) at room temperature first and then under reflux (120°), for ½ hr. The brown mixture was poured into excess ice water and stirred vigorously when the product (13·4 g, 85%) separated as pale brown solid, m.p. 193–194° (CH_2Cl_2). (Found: C, 68·70; 4·97; 3·70; Cl, 9·78. $C_{21}H_{18}ClNO_3$ requires: C, 68·51; H, 4·89; N, 3·80; Cl, 9·66%).

6-Chloro-8-hydroxy-2-methoxy-7,8,9,10-tetrahydrophenanthridine (**5b**). To benzoate **5a** (10 g, 0·0271 mole) in 100 ml of abs. EtOH was added 100 ml of alcoholic KOH (10%). The mixture was heated under reflux for 40 min, and cooled. The dark brown solution was poured on excess ice and stirred when a light brown precipitate was obtained (7·3 g, 95%) m.p. 157–158° (EtOH) ν_{max} 3450 cm^{-1}. (Found: C, 63·57; H, 5·51; N, 5·09; Cl, 13·09. $C_{14}H_{14}ClNO_3$ requires: C, 63·75; H, 5·31; N, 5·31; Cl, 13·47%).

6-Chloro-2-methoxy-8-tosyloxy-7,8,9,10-tetrahydrophenanthridine (**5c**). A solution of 6-chloro-8-hydroxy-2-methoxy-7,8,9,10-tetrahydrophenanthridine (**5b**) (660 mg, 0·0024 mole) and *p*-TsCl (480 mg, 0·0026 mole) in 10 ml of anhydrous pyridine was stirred at room temperature for 15 hr and poured onto ice-cooled HCl. The resulting precipitate was filtered and crystallized (C_6H_6—MeOH), m.p. 180°; yield 620 mg (60%). NMR ($CDCl_3$) τ: 2·0–3·1 (m, 7H), 42·8 (m, 1H) 6·1 (s, 3H), 7·0 (m, 4H), 7·56 (s, 3H), 7·75 (m, 2H). (Found: C, 60·07; H, 5·00; N, 3·10. $C_{21}H_{20}ClNO_4S$ requires: C, 60·36; H, 4·78; N, 3·35%).

8-Hydroxy-2-methoxy-7,8,9,10-tetrahydrophenanthridine (**5d**). To a solution of 2 g (0·0076 mole) of chloro-compound **5b** in 200 ml EtOH were added 650 mg of 10% Pd/C and 15 ml of 1N NaOH aq. The contents were shaken under H_2 (40 psi) for 20 hr. After the usual workup 1·8 g (100%) of product was obtained m.p. 157°. ν_{max} 3450, 1610 cm^{-1}. (Found: C, 73·57; H, 6·64; N, 5·95. $C_{14}H_{15}NO_2$ requires: C, 73·34; H, 6·59; N, 6·11%).

2-Methoxy-8-tosyloxy-7,8,9,10-tetrahydrophenanthridine (**5e**). To a solution of 229 mg (0·001 mole) of alcohol **5d** in 1·6 ml of pyridine were added 200 mg of *p*-TsCl. The contents were stirred overnight and decomposed on ice–water when 200 mg (52%) of the product was obtained, m.p. 162° (C_6H_6—MeOH).

ν_{max} 1625, 1175 cm^{-1}. NMR (DMSO-d_6) τ: 1·7 (s, 1H); 2–3 (m, 7H); 6·2 (s, 3H); 6·5 (m, 1H); 7 (m, 4H); 7·35–8·35 (5H). (Found: C, 66·02; H, 5·46; N, 3·57; S, 8·22. $C_{21}H_{21}NO_4S$ requires: C, 65·78; H, 5·52; N, 3·65; S, 8·35%).

8-Chloro-2-methoxy-7,8,9,10-tetrahydrophenanthridine (**5f**). To a solution of 2 g LiCl in 18 ml of DMF were added 0·9 g (0·0023 mole) of tosylate **5e** and the contents heated at 80° for 3 hr. Sufficient water was added to the mixture and the product $CHCl_3$ extracted. Solvent removal followed by chromatography through neutral alumina using CH_2Cl_2 as eluant gave 473 mg (76%) of product m.p. 123° (ether) ν_{max} 1615 cm^{-1}. NMR ($CDCl_3$) τ: 1·5 (broad, 1H); 2 (d, 1H); 2·8 (m, 2H); 5·5 (m, 1H), 6·1 (5, 3H); 6·75 (m, 4H); 7·75 (m, 2H). (Found: C, 68·04; H, 5·76; 5·45. $C_{14}H_{14}ClNO$ requires: C, 67·87; H, 5·65; N, 5·65%).

Hydroboration of 6-chloro-2-methoxy-8-pyrrolidino-9,10-dihydrophenanthridine. Boron trifluoride etherate (3·0 g, 50%) was added dropwise to a suspension of LAH (0·56 g, 0·14 mole) in dry ether (50 ml) at ice bath temperature. A slow stream of dry N_2 swept B_2H_6 generated into the flask containing 3·14 g (0·01 mole) of the enamine (**10b**) in 30 ml of dry THF at room temperature. The mixture was then stirred at room temperature overnight, evaporated under reduced pressure to a dark brown oily residue and dissolved in 50 ml of abs. EtOH. To this solution NaOH (1·5 g) and 5 ml of H_2O_2 (30%) were added. The mixture was heated under reflux for $\frac{1}{2}$ hr. The solvent was removed to give a brown oil which was taken up in $CHCl_3$ and washed with water thoroughly to remove all inorganic impurities. The $CHCl_3$ layer was dried ($MgSO_4$), solvent removed under reduced pressure and a dark brown oil obtained (2·0 g). Chromatography over neutral alumina using C_6H_6–$CHCl_3$ mixture (50:50) afforded a pale yellow crystalline solid (400 mg), identified spectroscopically as 2-methoxy-6-chloro-8-pyrrolidino-7,8,9,10-tetrahydrophenanthridine; M^+ at *m/e* 316. Further elution with $CHCl_3$ afforded 500 mg of 6-chloro-8-hydroxy-2-methoxy-7,8,9,10-tetrahydrophenanthridine (**5b**) as a colorless crystalline solid, identical to the previously prepared sample.

6-Chloro-2-methoxy-8-oxo-7,8,9,10-tetrahydrophenanthridine (**6**). The hydroxy compound **5b**, (9·54 g, 0·004 mole) was taken in 300 ml of acetone and freshly prepared Jones reagent added until the orange red color persisted. The mixture was stirred for a few min at room temp and poured into excess ice-water and vigorously stirred. A pale brown solid immediately precipitated, was collected, washed with distilled water and recrystallized from DMF—MeOH, m.p. 230° (8·35 g, 80%), ν_{max} 1720 cm^{-1}. (Found: C, 64·40; H, 4·60; N, 5·23; Cl, 13·58. $C_{14}H_{12}ClNO_2$ requires C, 64·24; H, 4·58; N, 5·35; Cl, 13·57%).

6-Chloro-2-methoxy-phenanthridine (**7**). The tetrahydrophenanthridine **5c** (417 mg, 0·001 mole) was added to a stirred solution of t-BuOk (226 mg, 0·001 mole) in 15 ml DMF under N_2 and stirred for 4 hr at room temp. The mixture was poured into water, $CHCl_3$ extracted and the organic layer washed with water and dried ($MgSO_4$). Removal of solvent provided **7** as a pale yellow solid; NMR ($CDCl_3$) τ, 1·9–3·0 (m, 7H), 6·1 (s, 3H). Absence of olefinic or methylene protons and appearance of four extra aromatic protons indicated the formation of aromatized structure **7**. Mass spectrum M^+ at *m/e* 243.

2-Methoxy-6,8,-dioxo-5,6,7,8,9,10-hexahydrophenanthridine (**8a**). A solution of 7·68 g of pyridine–sulfur trioxide complex in 40 ml of DMSO was added to a mixture of 4 g (0·0016 mole) of alcohol **4c** in 40 ml of DMSO containing 28 ml of Et_3N at 25°. After 10 min the contents were acidified with AcOH and poured into excess ice–water. The yellow solid was filtered and washed with sufficient water to give 2·5 g (63%) of product, m.p. 240°. ν_{max} 1724, 1667 cm^{-1}. NMR (DMSO-d_6) τ: 2·9 (m, 3H); 6·15 (s, 3H); 6·7 (m, 6H). Mass spectrum showed M^+ at *m/e* 243.

2-Methoxy-6,8-dioxo-5,6,7,8,9,10-hexahydrophenanthridine oxime (**8b**). To a mixture of 486 mg (0·002 mole) of ketone **8a** containing 0·175 g (0·005 mole) of hydroxylamine hydrochloride in 10 ml of EtOH aq, was added a solution of 125 mg of $NaHCO_3$ in 1 ml of water. The contents were warmed to dissolve the ketone and stirred at room temp for two hr. Addition of excess water provided 320 mg (63%) of product, m.p. 225–230°. ν_{max} 3333, 1615 cm^{-1}. NMR (DMSO-d_6) τ: 2·9 'm, 5H); 6·25 (s, 3H); 6·5–7·0 (m, 6H). Mass spectrum, M^+ at *m/e* 258.

8-Amino-6-hydroxy-2-methoxy-phenanthridine (**9**). The oxime **8b**. (400 mg) was heated with 8 g of polyphosphoric acid at 120° for 15 min., cooled and poured into ice–water giving 300 mg of a solid, m.p. 280–290°. Sublimation gave 70 mg (33%) of analytically pure **9**, m.p. 310°. ν_{max} 3450, 3225, 1667, 1613 cm^{-1}. NMR (DMSO-d_6) τ: 1·9 (s, 1H); 2·3–3·2 (m, 6H); 6·2 (s, 3H); 6·78 (m, 2H). (Found: C, 70·15; H, 5·16; N, 11·51. $C_{14}H_{12}N_2O_2$ requires: C, 70·00; H, 5·03; N, 11·66%).

6-Chloro-2-methoxy-8-pyrrolidino-9,10-dihydrophenanthridine (**10b**). The ketone **6** (5·0 g, 0·0019) in 200 ml of dry C_6H_6, 2·5 g (0·0035 mole) of pyrrolidine and 0·1 g of *p*-TsOH were heated under reflux using a water separator. The mixture became greenish brown. After heating under reflux overnight, solvent was removed and excess of pyrrolidine removed by evaporating the mixture under reduced pressure using fresh quantities of dry C_6H_6. The product was obtained as olive green crystalline needles, m.p. 160°. IR and NMR

spectra were consistent with the structure. Material could not be obtained analytically pure as it decomposed on repeated crystallization. Mass spectrum: M^+ at *m/e* 314.

7-Benzyl-6-chloro-2-methoxy-8-oxo-7,8,9,10-tetrahydrophenanthridine (**11**). 2-Methoxy-6-chloro-8-pyrrolidino-9,10-dihydrophenanthridine (**10b**, 1·57 g, 0·0005 mole) was dissolved in dioxane and BzCl slowly added. The mixture was heated under reflux for 12 hr, then taken up in benzene, washed with water, dried ($MgSO_4$) and solvent removed under reduced pressure. The residue (1·2 g) thus obtained was subjected to chromatography over neutral alumina. The first three fractions (C_6H_6 elution) gave a gummy material which was discarded. Elution with $CHCl_3$—C_6H_6 (20 : 80) mixture gave yellow crystals of the title compound (500 mg, 59%) further purified by recrystallization from $CHCl_3$–hexane, m.p. 154°. (Found: C, 71·51; H, 4·98; N, 4·03. $C_{12}H_{18}ClNO_2$ requires: C, 71·59; H, 5·11; N, 3·98%).

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