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REDUCED QUINOLINES AND QUINOLINIUM COMPOUNDS—I

REDUCTION OF QUINOLINE ANALOGS OF MODEL COMPOUNDS FOR COENZYME I* [1]

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Abstract—The reduction of quinoline analogs of model compounds for coenzyme I was investigated. The reaction of 1-benzyl-3-carbamidoquinolinium chloride (I) with alkaline sodium dithionite yielded predominantly a stable product which was shown to be sodium 1-benzyl-1,4-dihydro-3-carbamido-4-quinoline sulfonate (II). Compound II was also obtained from the reaction of I with alkaline sodium bisulfite. The reaction of II with sodium dithionite yielded 1-benzyl-1,4-dihydro-3-carbamidoquinoline (III).

When II was treated with a variety of acids, a new compound (V) was obtained and identified as 1-benzyl-3-carbamidoquinolinium 1-benzyl-1,4-dihydro-3-carbamidoquinoline-4-sulfonate. This compound was also obtained from the reaction of I with aqueous sulfur dioxide or thionyl chloride and pyridine or aqueous sodium bisulfite.

1-Methyl-3-carbamidoquinolinium iodide (VI) was reduced by alkaline sodium dithionite to yield 1-methyl-1,4-dihydro-3-carbamidoquinoline (VII). Compound VII reduced hexachloroacetone to hexachloroisopropanol in 10% yield.

THE reduction of NAD(DPN) to NADH with sodium dithionite has been known to take place with the appearance of a transient color. The mechanism of this reduction has received considerable attention since the postulation of an intermediate possessing a sulfinate group in the 4-position of the dihydropyridine ring of NADH.[2] The reduction of a NAD model, in which the group attached to N was 2,6-dichlorobenzyl, with the same reagent yielded a product which was formulated as a 1,2-sulfinate.[3] Kosower and Bauer have postulated that the intermediate in the dithionite reduction of a pyridinium ring is a charge-transfer complex between a sulfoxylate ion donor and a pyridinium ion acceptor.[4] More recently, Caughey and Schellenberg reinvestigated the reduction of N-benzylnicotinamide and isolated as their sole product an unstable yellow solid which they formulated as a 1,4-sulfinate or sulfoxylate addition product.[5] These authors consider their results as evidence for the postulation of the yellow intermediate in the dithionite reduction of NAD as an addition product rather than a charge-transfer complex. Similar results have been obtained by other workers, based on NMR studies of an intermediate which they formulate as a 1-benzyl-1,4-dihydro-3-carbamido-4-pyridine sulfinate.[6]

The reduction of analogous model compounds for NAD containing the quinolinium ring with or without a 3-carbamido group has been attempted but the results were

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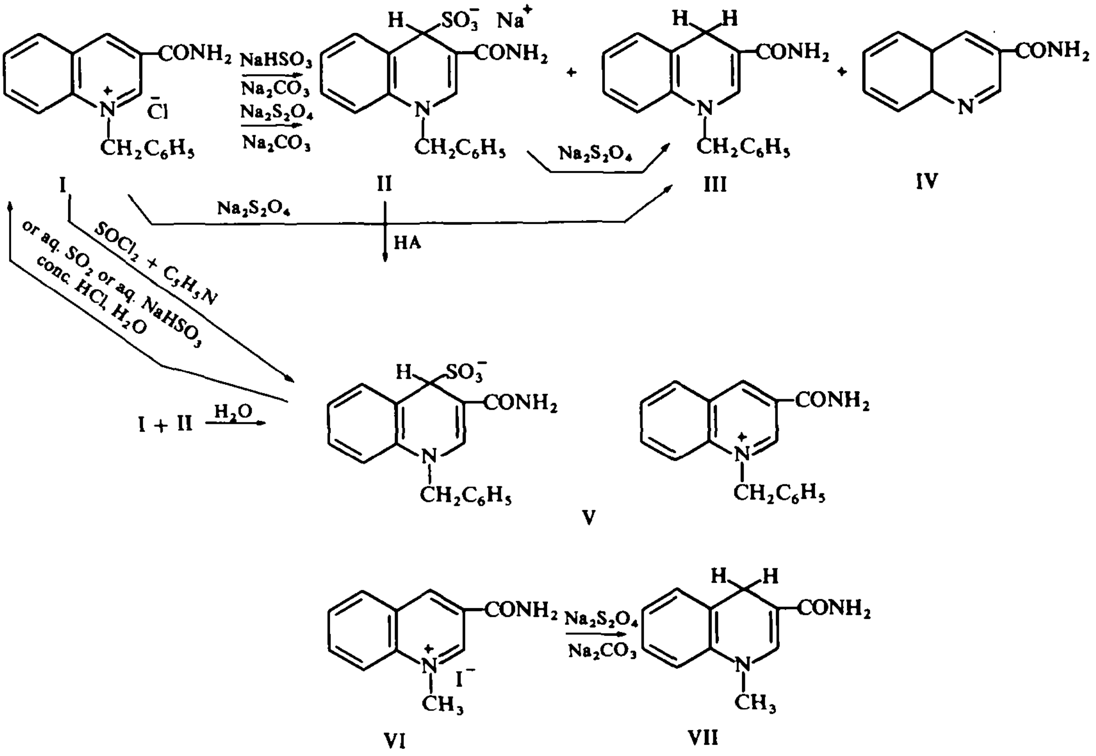
inconclusive.[7, 8] Unsuccessful attempts were made to characterize products from the reaction of 1-substituted quinolinium salts with sodium dithionite.[9] The reduction of 1-methylquinolinium iodide with the same reagent did not yield dihydro derivatives.[10]

We have investigated the reduction of N-substituted-3-carbamidoquinolinium salts with sodium dithionite. The results obtained are shown in Scheme I.

SCHEME I



HA = HCl, CH_3CO_2H, CF_3CO_2H, $HClO_4$, H_2SO_3

RESULTS

When a solution of 1-benzyl-3-carbamidoquinolinium chloride was added to an alkaline solution of sodium dithionite there was an instantaneous formation of an orange color which faded on continuous stirring. Three products were isolated: sodium 1-benzyl-1,4-dihydro-3-carbamido-4-quinolinesulfonate (II), 1-benzyl-1,4-dihydro-3-carbamidoquinoline (III), and 3-carbamidoquinoline (IV)* (Scheme I).

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* To eliminate the possibility of having compound IV present as an impurity in the starting material, some experiments were carried out using an aqueous solution of I. Compound IV is practically insoluble in water.

The evidence obtained from elemental analysis, mol wt. UV, IR and NMR spectra supported the structure assigned to II. The chemical reactions of II were also consistent with this structure. The IR spectra of II and III are shown in Fig. 1. Attempts to obtain acceptable analytical data for III failed because of its instability. Although this compound was not obtained analytically pure, meaningful spectra could be obtained. Compound III reduced an aqueous solution of silver nitrate and was oxidized by iodine to 1-benzyl-3-carbamidoquinolinium iodide. A bright red picrate was formed when III was treated with picric acid.

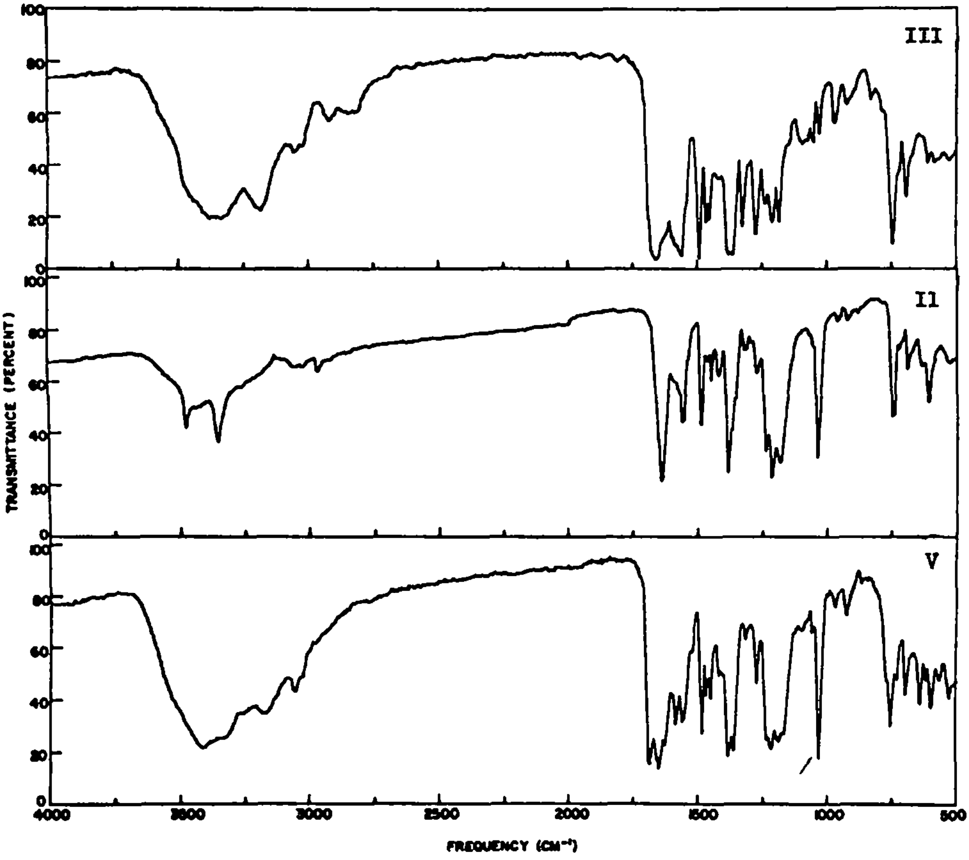

FIG. 1. Infrared spectra (KBr disk) of compounds III, II and V.

When sodium dithionite was added to a solution of I in water, in the absence of carbonate, an instantaneous orange color which faded was produced. A pale greenish-yellow product identified as III, was the only compound isolated.

When compound I was added to an alkaline solution of sodium bisulfite, the same transient color was observed and II was isolated. In the absence of carbonate, a yellow compound identified as V was obtained. The structure of V was established from its elemental analysis, mol wt, IR (Fig. 1) and UV spectra. The chemical reactions of V (Scheme I) were consistent with the assigned structures. Compound V was also obtained when II was treated with a variety of acids. When an aqueous solution of I was treated with an aqueous solution of sulfur dioxide or with thionyl chloride,* a product identified as V was obtained. In both instances there was the instantaneous appearance of a color which faded with the formation of a yellow product. Compound V yielded I when treated with concentrated hydrochloric acid.

The only product isolated from the reduction of 1-methyl-3-carbamidoquinolinium iodide (VI) with alkaline sodium dithionite was 1-methyl-1,4-dihydro-3-carbamidoquinoline (VII). The structure of this compound was assigned on the basis of its IR, UV and NMR spectra. Compound VII acted as a reducing agent towards methyl iodide, iodine, and hexachloroacetone. An orange picrate was formed on reaction with picric acid.

DISCUSSION

The results obtained in the present work are different from those reported by previous investigators. Several explanations may be put forward to explain the formation of II. This compound could result from the oxidation of the corresponding sulfinate. Another possibility is that II could have resulted from the presence of bisulfite as an impurity in dithionite. This possibility was eliminated by the fact that I and sodium dithionite in the absence of carbonate yielded III rather than V. Since II also resulted from the reaction of I with alkaline sodium bisulfite, II may result from the attack of sulfite ion rather than sulfinate or sulfoxylate ion on I. The color observed in both reactions could result from the formation of a charge-transfer complex between the electrophilic quinolinium ion and sulfite as a donor ion. Compound II could be the intermediate which would result from the slow formation of a covalent bond between the two ions. Some support for considering II an intermediate is given by the reaction of II with aqueous dithionite which yielded III. The reaction of I with sodium dithionite, in the absence of carbonate, yielded III. Previous investigators[3–5] have claimed that the intermediates, postulated either as activated complexes or as addition products, are decomposed by hydrogen ions to the corresponding dihydro compounds. However, under these conditions, our intermediate yielded a new compound formulated as V.

The formation of V from II and hydrogen ions is preceded by the rapid appearance of an orange color. This may be explained by the loss of sulfur dioxide from II. In a medium close to pH 7, sulfur dioxide remains dissolved and the sulfurous acid immediately complexes to give an orange color which is rapidly lost to give V.

The reactions of I and aqueous sulfur dioxide, or aqueous sodium bisulfite, or thionyl chloride and pyridine,* which all give rise to a similar orange color, followed by the formation of V, suggest the existence of a charge-transfer complex. Compound V is formed in aqueous solutions whose pH is between 5 and 7. Above pH 7, II is produced, below pH 5, sulfur dioxide is rapidly lost and I is obtained.

Compound V should result from the reaction of I and II. When aqueous solutions of these compounds were mixed no reaction could be observed. However, when water was gradually added to an equimolar mixture of solids I and II, an orange

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* The solution of I contained a few drops of pyridine which removed the hydrochloric acid formed on hydrolysis of thionyl chloride. In the absence of pyridine there was neither the appearance of a color nor the formation of a ppt.

color appeared and V was obtained. The reduction of 1-methyl-3-carbamidoquinolinium iodide (VI) with alkaline sodium dithionite was also preceded by the formation of an orange color. Only the corresponding dihydro compound (VII) was isolated from the yellow solution. It is clear from these observations that the type of reduced product obtained from quinolinium salts and dithionite is strongly dependent on the pH of the solution and the structure of the quinolinium salt. Our results suggest that the reduction of quinolinium salts with dithionite may proceed with the formation of a charge-transfer complex which breaks down rapidly to yield 1,4-dihydroquinolines. Further work is in progress to substantiate the existence of such a complex.

EXPERIMENTAL[*]

Preparation of salts

A. N-*Benzyl-3-carbamidoquinolinium chloride* (I). A mixture of 10 g (0·056 mole) 3-carbamidoquinoline[11] and 7·6 g (0·06 mole) benzyl chloride in 35 ml EtOH was refluxed for 4 hr, in the absence of moisture, and then for another 4 hr with more benzyl chloride (3·8 g, 0·03 mole) in 15 ml EtOH. The reaction mixture was treated with 50 ml diethyl ether and the colorless crystals formed were collected by filtration. Unreacted starting material was extracted with 2-propanol and the desired product recrystallized from 75% EtOH to yield 10 g (65% yield) of I, m.p. 218–221°. (Found: C, 68·41; H, 5·10; Cl, 11·83; N, 9·35. $C_{17}H_{15}ClN_2O$ requires: C, 68·30; H, 5·02; Cl, 11·90; N, 9·40%.) The IR spectrum (KBr disk) showed absorptions at 3400 (broad), 3240, 3180, 3060, 2950 (N—H and C—H), 1675, and 1625 cm^{-1} (amide), in addition to bands typical of the benzyl group and quinoline ring. The UV spectrum (95% EtOH) had λ_{max} 243 mμ (ε 20,000), and 322 mμ (ε 6010). The NMR spectrum in D_2O showed absorption at τ 0·6 (2-proton), 0·9 (s, 8-proton), 1·86 (m, 4 remaining quinoline protons), 2·88 (s, 5 aromatic ring protons), and 3·82 (s, 2 benzylic protons).

B. N-*Methyl-3-carbamidoquinolinium iodide* (VI). The procedure followed was that of Karrer and Stare.[12] The solid was recrystallized from 44% EtOH to give yellow crystals, m.p. 280–281° dec. (Found: C, 41·99; H, 3·51; I, 40·54; N, 8·85. $C_{11}H_{11}IN_2O$ requires: C, 42·03; H, 3·35; I, 40·44; N, 8·91%.) The IR spectrum (KBr disk) showed absorptions at 3350 (broad), 3170, 3070, 3000, 2965, 2945 (N—H and C—H), 1675, and 1625 cm^{-1} (amide), in addition to bands typical of the Me group and quinoline ring. The UV spectrum (95% EtOH) had λ_{max} 242 mμ (ε 24,800), and 321 mμ (ε 5000).

Reactions of N-*benzyl 3-carbamidoquinolinium chloride* (I)

A. *With sodium dithionite* (1). The procedure of Mautzerall and Westheimer was followed up to the separation step.[13] The reaction mixture was kept at −15° for 3 days. The solid formed was removed by filtration and shaken with 450 ml $CHCl_3$ for 3 days at room temp. The undissolved material was collected and extracted with 350 ml $CHCl_3$ in a continuous extractor for 7 hr. The combined $CHCl_3$ extracts were evaporated to dryness and treated with 15 ml $CHCl_3$ to yield 0·8 g (22% yield) of IV, m.p. 198–199° (lit.[14] m.p. 198–199°). Evaporation of the $CHCl_3$ extracts produced 1·6 g (29% yield) of III as a pale greenish-yellow solid, m.p. 150–151° dec (sintered at 127°). The undissolved material first obtained weighed 3·23 g (42% yield), and was recrystallized from 44% EtOH to give colourless needles of II, m.p. 239–241° dec.

2. To a soln of 1·95 g (0·011 mole) sodium dithionite in 20 ml distilled water, under an atm of N_2, was added portionwise, with stirring, 1·49 g (0·005 mole) of I over a period of 1 min. There was an instantaneous transient orange color. The resulting reddish-brown slurry was stirred with 40 ml $CHCl_3$. The mixture was stirred for 1 hr during which time two clear layers formed. The $CHCl_3$ layer was separated, dried, and evaporated to yield 1·08 g (76% yield) of III as a pale greenish-yellow solid. The aqueous layer was chilled at −15° for 2 days to yield II (8% yield).

B. *With sulfur dioxide.* A cooled, saturated aqueous soln of SO_2 was added dropwise to a stirred soln of 1·0 g (0·0033 mole) of I in 40 ml water. A transient orange color appeared immediately. The addition was

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[*] M.ps were taken on a Thomas–Hoover m.p. apparatus. IR spectra were determined on a Perkin–Elmer double beam 521 recording spectrophotometer, and UV spectra were recorded on a Perkin–Elmer model 202 spectrophotometer. NMR spectra were determined on a Varian Associates Model HR-60 or HA-60 spectrometer. Analyses were performed by Galbraith Laboratories, Knoxville, Tennessee and by Microanalytical Laboratories, Max-Planck Institute, 433 Mulheim (Ruhr), West Germany. Mol wts were determined by osmometry.

stopped when a few more drops of SO_2 soln did not produce the orange color. A yellow solid precipitated within 2 min and was collected to yield 0·5 g (51% yield) yellow needles, m.p. 189–191° dec., identified as V. (Found: C, 66·61; H, 5·08; N, 9·26; S, 5·34. $C_{34}H_{30}N_4SO_5\cdot 1/2H_2O$ requires: C, 66·34; H, 5·04; N, 9·10; S, 5·20%.) The IR spectrum of this compound was identical with that of the product obtained by treatment of II with acids.

C. *With thionyl chloride.* $SOCl_2$ was added dropwise to a stirred soln of 1·0 g (0·0033 mole) of I in 40 ml water containing 4 drops pyridine. A transient color was observed as in B and addition was stopped when this color was no longer produced. Recrystallization of the solid formed from 44% EtOH yielded 0·5 g (51% yield) yellow crystals, m.p. 189–191° dec, characterized as V. The IR spectrum of this compound was identical with that of the product described in the preceding paragraph.

D. *With sodium bisulfite.* A mixture of 0·5 g (0·002 mole) of I and 0·087 g (0·0084 mole) $NaHSO_3$ in 120 ml water was stirred at 25° for 48 hr during which time a yellow ppt formed. It was identified as V. A sample was redried at 100° (2 mm) just prior to analytical determination. (Found: C, 67·14; H, 5·11; N, 9·19; S, 5·42. $C_{34}H_{30}N_4SO_5$ requires: C, 67·32; H, 4·95; N, 9·24; S, 5·28%.)

The IR spectrum of this compound was identical with that of the product described in the reaction B above.

E. *With alkaline sodium bisulfite.* The reaction was performed as described in D but using 0·5 g (0·005 mole) Na_2CO_3, 0·18 g (0·002 mole) $NaHSO_3$ and 0·5 g (0·002 mole) of I in 25 ml water. The solid obtained (0·58 g, 90% yield) was identified as II, m.p. 239–241° dec. A sample was redried at 100° (2 mm) just prior to analytical determination. (Found: C, 55·69; H, 4·31; N, 7·76; Na, 6·09; S, 8·94. $C_{17}H_{15}N_2NaSO_4$ requires: C, 55·74; H, 4·09; N, 7·65; Na, 6·28; S, 8·74%.) The IR spectrum of this compound was identical with that of the product obtained by treatment of I with alkaline sodium dithionite.

Reactions of 1-*benzyl*-1,4-*dihydro*-3-*carbamidoquinoline* (III)

Compound III was unstable in air in either water or $CHCl_3$ soln. This material was isolated as a pale greenish-yellow powder after repeated reprecipitations from $CHCl_3$ soln with pet.-ether (30–60°), m.p. 150–151° dec. (sintered at 127°). All purification attempts failed to yield an analytically pure sample. The IR spectrum (Fig. 1) as a KBr disk showed absorptions at 3350 (broad), 3180, 3060, 3020, 2960, 2920, 2821, (N—H and C—H), 1660 (broad) (amide) and 1560 cm^{-1} (vinylogous amide) in addition to bands typical of the benzyl group and quinoline ring. A much better spectrum may be obtained in $CHCl_3$ which show absorptions at 3525, 3410 (free N—H), 1675, 1615 (amide), 1595, 1580, and 1565 cm^{-1} (vinylogous amide). The UV spectrum (95% EtOH) had λ_{max} 234 mμ (ε 9360), and 340 mμ (ε 7180). The NMR spectrum in $CDCl_3$ showed absorption at τ 3·32 (m, 10 protons, Ph ring and 2, 5, 6, 7, 8 protons of quinoline ring, 4·60 (s, 2 amide protons), 5·46 (s, 2 benzylic protons), and 6·34 (s, 2 protons of 4-methylene).

A. *With picric acid.* Compound III formed a picrate when treated with picric acid in 95% EtOH. This salt was recrystallized from 44% EtOH to give bright orange plates, m.p. 150–152° dec. (Found: C, 56·08; H, 3·92; N, 14·32. $C_{23}H_{19}N_5O_8$ requires: C, 55·98; H, 3·85; N, 14·19%.)

B. *Oxidation reactions.* When III was added to a warm 10% $AgNO_3$ aq a black ppt was obtained. When III was treated with a soln of I_2 in $CHCl_3$ according to the procedure of Saunders and Gold[15] the corresponding quinolinium salt was obtained. It was recrystallized from MeOH-diethyl ether to give bright yellow needles, m.p. 209–212° dec. (Found: C, 52·27; H, 3·93; I, 32·43; N, 7·10. $C_{17}H_{15}IN_2O$ requires: C, 52·30; H, 3·84; I, 32·50; N, 7·17%.)

Reactions of sodium 1-*benzyl*-1,4-*dihydro*-3-*carbamido*-4-*quinolinesulfonate* (II)

This material was recrystallized from 44% EtOH to give white needles, m.p. 239–241° dec. The pure product was obtained in some hydrated stage and the analytical data varied with the water of crystallization. (Found: C, 51·67; H, 4·59; N, 7·35; Na, 6·16; S, 8·47. $C_{17}H_{15}N_2NaSO_4\cdot 1{\cdot}5H_2O$ requires: C, 51·90; H, 4·58; N, 7·12; Na, 5·88; S, 8·14%; Found: C, 53·23; H, 4·64; N, 7·29; Na, 6·01; S, 8·35. $C_{17}H_{15}N_2NaSO_4\cdot H_2O$ requires: C, 53·20; H, 4·43; N, 7·29; Na, 6·01; S, 8·35%.) A sample was redried at 100° (2 mm) just prior to analytical determination. (Found: C, 55·63; H, 4·32; N, 7·84; Na, 6·15; S, 8·64. $C_{17}H_{15}N_2NaSO_4$ requires: C, 55·74; H, 4·09; N, 7·65; Na, 6·28; S, 8·74%.)

A mol wt determination in water gave a value of 364 (calc. 366). The IR spectrum (Fig. 1), as a KBr disk, showed absorptions at 3475, 3350, 3060, 3030, 2965 (N—H and C—H), 1640, (amide) and 1560 cm^{-1} (vinylogous amide) in addition to bands typical of the benzyl group and quinoline ring. Strong bands at 1240, 1215, 1180 and 1040 may be assigned to the sulfonate group. The UV spectrum (95% EtOH) of II showed maxima at 240 mμ (ε 8,600) and 332 mμ (ε 8,020). The NMR spectrum in d_6-dimethylformamide showed absorption at τ 2·92 (m, 12 protons from amide group, Ph and 2, 5, 6, 7, 8-protons of quinoline rings), 5·02 (s, 2 benzylic protons), and 5·25 (s, 4-H proton).

A. *With acids.* A variety of acids (Scheme I) was added to II to yield V. The following procedure is representative of all these reactions. A soln of 1·0 g (0·0026 mole) of the monohydrate of II in 65 ml water was stirred and 3 to 5 drops of the acid were added dropwise to it. The colorless soln turned orange immediately and a yellow solid formed after a few min. Recrystallization from 44% EtOH produced yellow needles, m.p. 190–191° dec, yields ranged from 50–88%. (Found: C, 66·55; H, 5·16; N, 9·05; S, 5·38. $C_{34}H_{30}N_4SO_5 \cdot \frac{1}{2}H_2O$ requires: C, 66·34; H, 5·04; N, 9·10; S, 5·20%.) Mol wt determinations in EtOH and MeOH gave values of 618, 640, 630. (Calc. 606). The IR spectrum as a KBr disk (Fig. 1) showed bands common to both I and II. The UV spectrum (95% EtOH) was also a composite of the spectra of these two compounds. it showed maxima at 242 mμ (ε 30,800), and 322 mμ (ε 15,400).

B. *With sodium dithionite.* A soln of 0·384 g (0·0010 mole) of II in 100 ml water, under an atm of N_2, was treated with stirring with 0·39 g (0·0022 mole) sodium dithionite added portionwise over a period of 30 sec. The reaction mixture was extracted with $CHCl_3$, the $CHCl_3$ layer dried and evaporated to yield 0·23 g (85% yield) of III, m.p. 150° dec. (sintered at 127°). The IR spectrum of this compound was identical with that of the product obtained by treatment of N-benzyl-3-carbamidoquinolinium chloride with sodium dithionite.

C. *With* I. To a mixture of 0·24 g (0·00064 mole) of II and 0·19 g (0·00064 mole) of I, 15 ml water was added portionwise. An orange color appeared immediately The soln was refluxed for 1 hr. Compound V (0·15 g, 75% yield) was collected by filtration from the cooled soln. The IR spectrum of this compound was identical with that of the product described in the reaction A above.

Hydrolysis of V. Con HCl was added dropwise, with stirring, to a suspension of 0·5 g (0·0008 mole) of V in 100 ml water, until a clear soln was obtained. The solvent was evaporated and the green residue left was extracted with hot EtOH. The extracts were treated with diethyl ether and a white ppt, m.p. 218–221°, identified as I was obtained. The IR spectrum of this compound was identical with that of the product obtained by treatment of 3-carbamidoquinoline with benzyl chloride.

Preparation of 1-methyl-1,4-dihydro-3-carbamidoquinoline (VII). A soln of 5·72 g (0·054 mole) Na_2CO_3 and 12·58 g (0·054 mole) sodium dithionite in 100 ml water was warmed to 50°, under an atm of N_2. Compound VI (6·28 g, 0·020 mole) was added portionwise, with stirring, to the above soln over a period of 7 min. There was an instantaneous transient orange color. The resulting soln was extracted with $CHCl_3$ in a continuous extractor. The extracts were dried and the solvent evaporated to give 1·8 g (50% yield) of a light yellow solid. This material did not display a definite m.p. but decomposed between 95 and 100°. Its IR spectrum (KBr disk) showed absorptions at 3450 (broad) 3325, 3060, 2920, 2940 (N—H and C—H), 1655, 1615 (amide), 1572, and 1550 cm^{-1}, (vinylogous amide) in addition to bands typical of the Me group and quinoline ring. The UV spectrum (95% EtOH) had λ_{max} 239 mμ (ε 11,400), and 334 mμ (ε 6,950). The NMR spectrum in $CDCl_3$ showed absorption at τ 2·94 (m, 7 protons, amide, and 2,5–8 protons of quinoline ring), 6·34 (s, 4-methylene protons), 7·10 (N-Me protons).

Reactions of VII

A. *With picric acid.* A soln of 1·0 g (0·0053 mole) of VII in 20 ml of a saturated 95% EtOH soln of picric acid was kept for 72 hr at 25°, under N_2. An orange solid precipitated. It was collected to yield 1·65 g (74% yield) of the picrate of VII. Recrystallization from 70% EtOH produced dark red needles, m.p. 194–196° dec. (Found: C, 49·14; H, 3·47; N, 16·64. $C_{17}H_{15}N_5O_8$ requires: C, 48·93; H, 3·62; N, 16·78%.)

B. *With methyl iodide.* This reaction was carried out according to the procedure of Saunders and Gold.[15] At the end of the reaction, the solid was collected by filtration. Recrystallization from MeOH-diethyl ether yielded bright yellow needles of VI, m.p. 280–281° dec. The IR spectrum of this compound was identical with that of the product obtained by treatment of 3-carbamidoquinoline with MeI.

C. *With hexachloroacetone.* This reaction was carried out by the procedure of Fouty and Dittmer.[16] The hexachloroisopropanol obtained was recrystallized from n-hexane to yield 0·1 g (10% yield) of dark tan tablets. m.p. 85–86° (lit.[17] m.p. 86–87°). The IR spectrum of this product was identical to a previously published spectrum of this compound.[18]

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