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Novel Heterocyclic Derivatives of Quinuclidine

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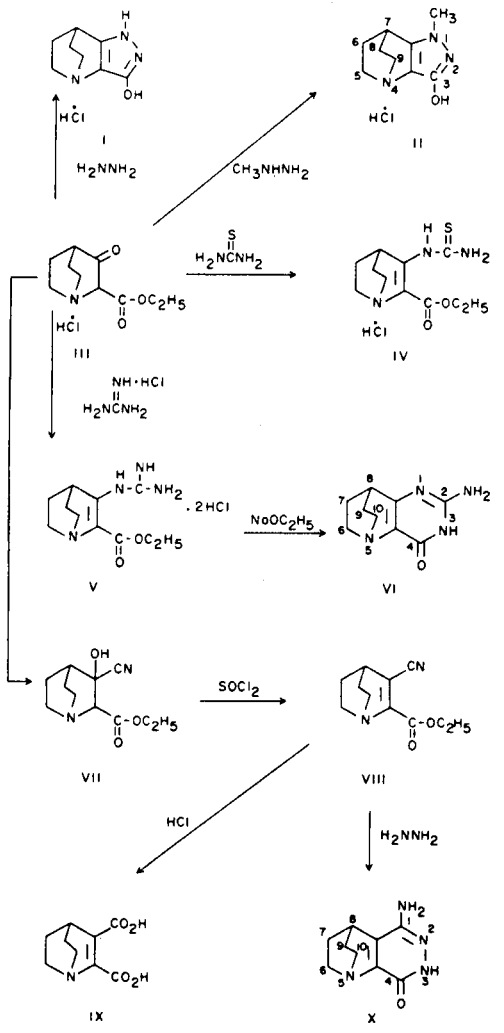
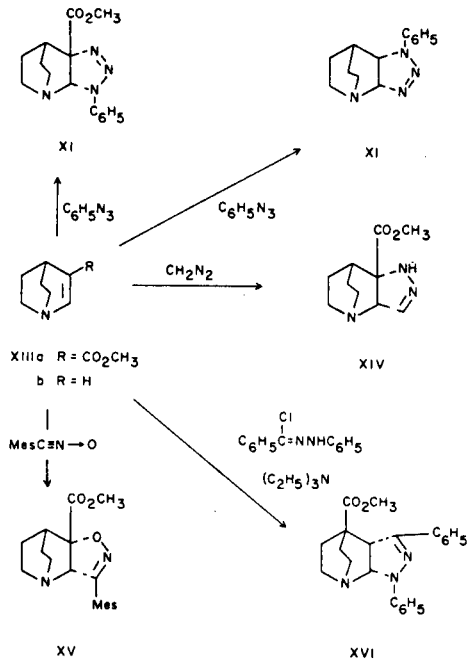
Treatment of ethyl 3-quinuclidinone-2-carboxylate (III) with appropriate reagents gave 2,3-fused heterocycles including pyrazolol, aminopyrimidinone, and aminopyridazinone types. The thiourea derivative of III could not be cyclized. Triazoline, pyrazoline, and isoxazoline derivatives were prepared by 1,3-dipolar cycloadditions to the 2- and 3-positions of methyl 2,3-dehydroquinuclidine-3-carboxylate (XIIIa). Such facile formation of cycloaddition products was not possible with 2,3-dehydroquinuclidine, which reacted only with phenylazide (in poor yield). Structural assignments for the products of cycloaddition were made by analogy, but alternative structures could not be ruled out by the nmr or mass spectra.

Although a variety of quinuclidine derivatives has been prepared (1), there appear to be no examples in which another heterocyclic ring is directly fused to this system. However, it is apparent that a number of interesting heterocyclic derivatives can, in principle, be prepared by condensation reactions with quinuclidines containing 1,3-dicarbonyl groups and by 1,3-dipolar cycloadditions to quinuclidines containing activated olefinic bonds. We were led to undertake the preparation of a variety of such derivatives not only by the prospect that they might possess interesting biological activities (2), but also by the possibility that the chemical transformations, particularly the cycloadditions, might further define the properties of the quinuclidine system.

The 1,3-dicarbonyl system of ethyl 3-quinuclidinone-2-carboxylate hydrochloride (III) (3) provided an attractive starting point for our purposes, and we therefore treated III with a variety of bifunctional nucleophilic reagents. Thus, condensation with hydrazine afforded pyrazole I as the hydrochloride, while condensation with methylhydrazine furnished methylpyrazole II as the hydrochloride. The assignment of hydroxypyrazole, rather than pyrazolone structures, to these products follows from their IR and UV spectra [λ max 6.25 μ; 240 mμ ($\epsilon \sim 4{,}000$)] which are unlike the spectra of model compounds fixed in the pyrazolone form by *C*-alkylation, but like the spectra of model pyrazolones free to assume the tautomeric hydroxypyrazole form (4). Structure II is based on the premise that the more nucleophilic methylated nitrogen of methylhydrazine should add first to the ketonic carbonyl of III; however, the alternate 2-methyl product is not ruled out by the experimental evidence. Treatment of III with thiourea





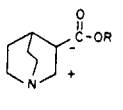
readily gave the 3-thiocarbamoylimino derivative IV, assigned the α,β-unsaturated ester structure because of λ max (MeOH), 240 mμ, but this derivative could not be cyclized. When it was heated in cumene at reflux temperature it underwent decomposition to a tarry material which had infrared absorption at 4.83 μ, indicative of the isothiocyanate group. Guanidine hydrochloride also condensed smoothly with III, and the resulting guanidino derivative V (dihydrochloride, assigned the α,β-unsaturated ester structure because of λ max (MeOH), 240 mμ) was cyclized to aminopyrimidinone VI upon treatment with two equivalents of sodium methoxide. It was not possible to remove by fractional crystallization or chromatography a mole of guanidine complexed with VI, although some loosely bound sodium chloride was separated by chromatography on a polystyrene resin. That the complex between VI and guanidine does not involve strong chemical bonds was shown by its mass spectrum, which had the molecular ion of VI at m/e 192 (no higher peaks) and peaks corresponding to the molecular ion of guanidine at m/e 59 and its principal decomposition fragment $H_2N\text{-}C \equiv NH^+$) at m/e 43. There was no peak at m/e 192–59, indicating that the presumed guanidine peak could not have been formed directly from fragmentation of the molecular ion of VI. The most likely structure for a complex which would be stable to crystallization, yet not strongly bound chemically, would be one involving hydrogen bonding between VI and guanidine. Unfortunately the insolubility of this complex in all solvents except water precludes careful study of such hydrogen bonding. Several attempts to prepare a pyrimidinedione by condensing III with urea were unsuccessful. There was apparent reaction of the ketonic carbonyl III with one of the urea nitrogens (infrared evidence), but the crude product could not be cyclized upon further heating.

Dehydration of cyanhydrin VII, prepared from III by the method of Rubtsov (5), furnished ethyl 3-cyano-2,3-dehydroquinuclidine-2-carboxylate VIII (6). Treatment of VIII with hydrazine readily afforded aminopyridazinone X.

For the preparation of heterocyclic derivatives of quinuclidine via the 1,3-dipolar cycloaddition method, methyl 2,3-dehydroquinuclidine-3-carboxylate (XIIIa) (7) proved to be a versatile starting material. It readily added phenyl azide, diazomethane, and 1,3-diphenylnitrileimine (8), affording the phenyltriazoline XI, pyrazoline XIV, and diphenylpyrazoline XVI derivatives, respectively. In assigning detailed structures to the cycloaddition products it is not possible to make an unequivocal choice between the depicted *cis*-structures and the alternate *cis*-structures derived from addition of the dipolar reagent in the opposite manner to the ends of the dipolarophile. The nmr spectra were of little value in this respect since we were unable to resolve them due to their complexity. A mass spectrum was obtained for the phenyltriazole XI, but it also provided no basis for distinguishing between the two possible structures, since the fragmentation pattern shown below is consistent with either structure. This spectrum is, nonetheless, of interest as an illustration of the properties of a quinuclidine derivative under electron impact.

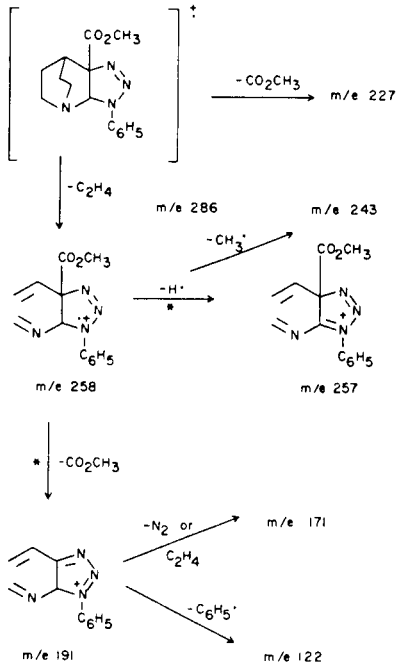
Prediction of the structures on mechanistic grounds is also difficult, since the mechanism(s) of the 1,3-dipolar addition reaction is not well understood. However, at least for the additions of azides, diazoalkanes, and nitrilylides to styrene, Huisgen concluded that three-membered ring intermediates are not involved and that the cycloadditions obey the Woodward-Hoffman selectivity rules for polycenter additions (only *cis*-addition allowed) (9).

If this conclusion may be applied to the present problem, then the most probable structures for concerted or nearly concerted cycloaddition to XIIIa would follow from the 1,3-dipolar forms of the reagents ($C_6H_5\text{-}\bar{N}\text{-}N{=}\overset{+}{N}$, $H_2\bar{C}\text{-}N{=}\overset{+}{N}$, and $C_6H_5\text{-}\overset{+}{\bar{C}}\text{=}N\text{-}\bar{N}\text{-}C_6H_5$) (10), assuming that the nitrileimine addition occurs in a similar mode, and the polarized form A of XIIIa, and they would be as depicted in XI, XIV, and XVI.



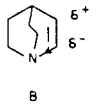
A

Treatment of XIIIa with benzonitrile oxide afforded only starting material and the dimer of benzonitrile oxide (10). However, as anticipated from the work of Grundmann and Dean (11), 2,4,6-trimethylbenzonitrile oxide



added readily to XIIIa, affording a mesitylisoxazoline in good yield. The structure of this product predicted from the interaction of resonance form A with the 1,3-dipolar form of the nitrile oxide would have the isoxazoline ring fusion opposite to the manner depicted by XV. However, since models show severe steric repulsion between the carbomethoxy and mesityl groups in both the form predicted on electronic grounds and in the assumed transition state leading to this form, we consider XV a more reasonable structure (12).

In the cycloaddition of 1,3-dipolar reagents to double bonds, the rate of reaction is in general enhanced by conjugation of the double bond or by strain which is relieved on saturation of the double bond (10). Only the most reactive 1,3-dipolar reagents add to a non-conjugated, relatively strain-free system such as found in cyclohexane (10). It was therefore of considerable interest to investigate the reaction of various 1,3-dipolar reagents with 2,3-dehydroquinuclidine (XIIIb) (13). This compound probably has a small degree of ring strain due to its bicyclic geometry. However, it should be much less activated by strain than, for example, norbornene. The overall effect of the tertiary nitrogen on the reactivity of the double bond is difficult to assess. Grob has convincingly demonstrated that, as anticipated from the bridgehead location of this nitrogen, it is unable to participate with the double bond in forming an enamine system (13). Hence the high reactivity of enamines toward dipolar reagents (10) would not be expected for XIIIb. The inductive effect of this nitrogen might increase reactivity, but there are no appropriate models on which to base an estimate of this effect. When XIIIb was treated with the same azide, diazoalkane, nitrile-imine, and nitrile oxide reagents which had reacted readily with XIIIa only one reaction, that with phenyl azide, occurred to an appreciable extent. In the other three examples only starting material was recovered. These results suggest a lack of important enhancement of double-bond reactivity by the ring-strain and nitrogen inductive effects operating in XIIIb. It is not possible to distinguish between alternative structures for the triazoline which is formed by reaction of XIIIb with phenyl azide; however, the depicted structure XII would be predicted on the basis of the inductive effect of the nitrogen in XIIIb, which would lead to polarized form B.



B

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide discs with a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform, unless otherwise specified, with a Varian A-60 spectrometer. Mass spectra were determined on an AE1 MS9 mass spectrometer at ionizing voltage 70 ev and source temperature 140°. Solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

3-Hydroxypyrazolo[4,3-*b*]quinuclidine Hydrochloride (I).

To 25 ml. of hydrazine hydrate was added gradually 7.0 g. of ethyl 3-quinuclidinone-2-carboxylate hydrochloride (III) (3). The resulting solution was heated at reflux temperature for 16 hours, then cooled. The crystals which formed on cooling were collected by filtration, and the filtrate was concentrated to give additional solid. A total yield of 3.5 g. (71%) of 3-hydroxypyrazolo[4,3-*b*]-quinuclidine (I), m.p. 273-278° was obtained; λ max 3.15, 6.25 μ; 238 mμ (ε, 1,900). This product was converted into its hydrochloride salt, m.p. 213-216°, by dissolving it in 30 ml. of 1 *N* hydrochloric acid and concentrating this solution to dryness.

Anal. Calcd. for $C_8H_{11}N_3O\cdot HCl$ (201.66): C, 47.64; H, 6.00; N, 20.84; Cl, 17.58. Found: C, 47.35; H, 5.91; N, 20.59; Cl, 17.91.

3-Hydroxy-1-methylpyrazolo[4,3-*b*]quinuclidine (II).

To 40 ml. of methylhydrazine was added gradually 9.35 g. of ethyl 3-quinuclidinone-2-carboxylate hydrochloride (III). The resulting clear solution was heated at reflux temperature for 4 hours and then concentrated. The glassy residue was dissolved in 50 ml. of water, neutralized with concentrated hydrochloric acid, partially concentrated and saturated with sodium chloride. A methylene chloride solution of the resulting precipitate was dried, filtered, and treated with hexane, whereupon a white precipitate formed in low yield. Recrystallization of this solid from the same solvents gave 3-hydroxy-1-methylpyrazolo[4,3-*b*]quinuclidine (II), m.p. 217-220°; λ max 6.25 μ, no absorption at 3.15 μ; 238 mμ (ε, 5,500).

Anal. Calcd. for $C_9H_{13}N_3O$ (179.22): C, 60.31; H, 7.31; N, 23.45. Found: C, 60.02; H, 7.41; N, 23.66.

Ethyl 2,3-Dehydro-3-(thiocarbamoylamino)quinuclidine-2-carboxylate (IV).

A mixture of 7.01 g. (30 mmoles) of ethyl 3-quinuclidinone-2-carboxylate hydrochloride (III), 2.28 g. (30 mmoles) of thiourea and 150 ml. of ethanol was heated at reflux temperature for 24 hours. The resulting solution was concentrated to *ca.* 75 ml., cooled to 5° and filtered. Further concentration of the filtrate afforded an orange semi-solid which slowly solidified to a glass on standing. This procedure gave ethyl 2,3-dehydro-3-(thiocarbamoylimino)quinuclidine-2-carboxylate (IV) as its hydrochloride ethanolate hydrate, a glass with indefinite m.p.; λ max 240 mμ (ε, 1,800). The presence of one mole of ethanol and one mole of water was indicated by the nmr spectrum of this sample.

Anal. Calcd. for $C_{11}H_{17}N_3O_3S \cdot HCl \cdot C_2H_5OH \cdot H_2O$ (355.89): C, 43.87; H, 7.36; N, 11.81; S, 9.01; Cl, 9.96. Found: C, 43.79. H, 7.55; N, 11.91; S, 9.40; Cl, 10.14.

The above described sample of IV was heated in chlorobenzene at reflux temperature for 16 hours. On cooling a dark semi-solid separated. This material had strong infrared absorption at 4.83 μ.

Ethyl 2,3-Dehydro-3-guanidinoquinuclidine-2-carboxylate (V).

A mixture of 7.01 g. (30 mmoles) of ethyl 3-quinuclidinone-2-carboxylate hydrochloride (III), 2.87 g. (30 mmoles) of guanidine hydrochloride and 50 ml. of ethanol was heated at reflux temperature for 110 minutes, then kept at room temperature for 3 days. During this time ethyl 2,3-dehydro-3-guanidinoquinuclidine-2-carboxylate (V) crystallized as its dihydrochloride, white prisms, m.p. 179-181°; λ max 240 mμ (ε, 1,900). Yield 6.58 g. (67%).

Anal. Calcd. for $C_{11}H_{20}N_4O_3 \cdot 2HCl$ (329.23): C, 40.13; H, 6.74; N, 17.02; Cl, 21.54. Found: C, 40.30; H, 6.13; N, 17.23; Cl, 21.51.

2-Amino-3*H*-pyrimidino[5,4-*b*]quinuclidin-4-one (VI).

A solution of 2.5 g. (7.6 mmoles) of ethyl 2,3-dehydro-3-guanidinoquinuclidine-2-carboxylate dihydrochloride (V) in 70 ml. of ethanol was treated with a solution of sodium ethoxide prepared from 0.385 g. (0.0168 g-atom) of sodium and 20 ml. of ethanol. After 30 minutes, the mixture was filtered to remove sodium chloride and the filtrate was heated at reflux temperature for 16 hours. Concentration of the resulting solution gave a white solid, which upon recrystallization from ethanol afforded 2-amino-3*H*-pyrimidino[5,4-*b*]quinuclidin-4-one (VI) as white crystals, m.p. 258°, a hemi-hydrate complexed with one mole of guanidine and contaminated with 8% of sodium chloride. The sodium chloride was removed by passing an aqueous solution of the product through Amberlite XAD-2 (14). The eluate was concentrated and the residue was crystallized from methanol. This procedure gave VI as white crystals, dec. 265°, complexed with one mole of guanidine and solvated with methanol. The mass spectrum showed the molecular ion at m/e 192 and important peaks at m/e 177, 164, 163, 150, 122, 59 and 43.

Anal. Calcd. for $C_9H_{12}N_4O \cdot CH_5N_3 \cdot CH_3OH$: C, 46.63; H, 7.47; N, 34.61. Found: C, 46.42; H, 7.20; N, 34.54.

Ethyl 3-cyano-2,3-dehydroquinuclidine-2-carboxylate Hydrochloride (VIII).

To 60 ml. of thionyl chloride chilled in an ice bath was added 7.46 g. of ethyl 3-cyano-3-hydroxyquinuclidine-2-carboxylate (VII) (5). The resulting solution was heated at reflux temperature for 16 hours, then concentrated to dryness. Adhering thionyl chloride was removed by concentration of two 10 ml. portions of benzene from the residue. The orange crystalline residue was recrystallized from ethanol, affording 4.0 g. (50%) of ethyl 3-cyano-2,3-dehydroquinuclidine-2-carboxylate hydrochloride (VIII) as white needles, m.p. 164.5-165.5°. An analytical sample, recrystallized from ethanol, had m.p. 166-167.5°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$ (242.71): C, 54.43; H, 6.23; Cl, 14.61; N, 11.54. Found: C, 53.68; H, 6.12; Cl, 14.26; N, 12.24.

2,3-Dehydroquinuclidine-2,3-dicarboxylic acid Hydrochloride (IX).

A mixture of 2.78 g. of ethyl 3-cyano-2,3-dehydroquinuclidine-2-carboxylate hydrochloride (VIII), 56 ml. of glacial acetic acid and 28 ml. of concentrated hydrochloric acid was heated at reflux temperature for 24 hours and then concentrated to dryness. The crystalline residue was recrystallized from ethanol, affording 2.03 g. (76%) of 2,3-dehydroquinuclidine-2,3-dicarboxylic acid hydrochloride (IX) as white needles, m.p. 235-237°. A further recrystallization from aqueous ethanol gave white needles, m.p. 239.5-240° (Lit. (6) m.p. 240°).

1-Amino-3*H*-pyridazino[4,5-*b*]quinuclidin-4-one (X).

A mixture of 0.95 g. of ethyl 3-cyano-2,3-dehydroquinuclidine-2-carboxylate hydrochloride (IX) and 20 ml. of hydrazine hydrate was heated at reflux temperature for 2 hours. The resulting solution was concentrated under reduced pressure until crystals formed and it was then chilled to 5°. This procedure gave 0.55 g. (73%) of crude 1-amino-3*H*-pyridazino[4,5-*b*]quinuclidine-4-one (X) as white needles. An analytical sample, recrystallized two times from ethanol, had m.p. 298-301°; λ max 223 (ε, 20,200), 323 mμ (ε, 2,490).

Anal. Calcd. for $C_9H_{12}N_4O$ (192.22): C, 56.23; H, 6.29; N, 29.15. Found: C, 56.23; H, 6.64; N, 28.98.

Methyl 3-Phenyl-*v*-triazol[1]ino[4,5-*b*]quinuclidine-7a-carboxylate (XI).

A solution of 1.31 g. (11 mmoles) of phenyl azide in hydrocarbon solution (15) was treated with 1.67 g. (10 mmoles) of methyl 2,3-dehydroquinuclidine-3-carboxylate (XIIIa) (7) and the mixture was heated at reflux temperature for 24 hours. It was then concentrated and the residue was treated with ether. The solid that formed was washed with a little cold methanol. This procedure gave 1.68 g. (59%) of methyl 3-phenyl-*v*-triazol[1]ino-[4,5-*b*]quinuclidine-7a-carboxylate (XI) as white crystals, melting with gas evolution at 137-141°. An analytical sample, recrystallized from methanol, melted with gas evolution at 143.5-145°. The principle peaks in the mass spectrum of this sample were at 286 (molecular ion), 258, 257 (metastable for 258 → 257 at 256), 243, 229 (metastable for 258-229 at 203), 227, 191 (metastable for 258 → 191 at 153.5), 171, 122 m/e.

Anal. Calcd. for $C_{15}H_{18}N_4O_2$ (286.33): C, 62.92; H, 6.34; N, 19.57. Found: C, 62.58; H, 6.01; N, 19.15.

3-Phenyl-*v*-triazol[1]ino[4,5-*b*]quinuclidine (XII).

This compound was prepared from 2,3-dehydroquinuclidine (13) by the procedure described for carbomethoxy analog XI. The yield was very low and the product had m.p. 160-163° with gas evolution.

Anal. Calcd. for $C_{13}H_{16}N_4$ (228.29): C, 68.39; H, 7.06; N, 24.54. Found: C, 68.31; H, 7.24; N, 24.28.

Methyl Pyrazol[2]ino[3,4-*b*]quinuclidine-3a-carboxylate Hydrochloride (XIV).

A solution of 1.13 g. (6.75 mmoles) of methyl 2,3-dehydroquinuclidine-3-carboxylate (XIIIa) (7) in 70 ml. of methylene chloride was treated with a solution of diazomethane [prepared from 1.99 g. (13.5 mmoles) of *N*-methyl-*N*-nitroso-*N'*-nitroguanidine] in 100 ml. of ether. After 40 hours the resulting solution was concentrated. The oily yellow residue was treated with anhydrous hydrogen chloride in ether, and the precipitate that formed was washed well with ether. This procedure afforded 1.18

g. (71%) of methyl pyrazol[2]ino[3,4-*b*]quinuclidine-3a-carboxylate hydrochloride (XIV) as white solid, m.p. 164-166°. An analytical sample, recrystallized from ethanol, had m.p. 173.5-174.5°.

Anal. Calcd. for $C_{10}H_{15}N_3O_2HCl$ (245.70): C, 48.88; H, 6.56. N, 17.10; Cl, 14.43. Found: C, 48.69; H, 6.55; N, 17.14; Cl, 14.35.

Methyl 3-[1-(2,4,6-trimethylphenyl)]isoxazol[2]ino[4,5-*b*]quinuclidine-7a-carboxylate Hydrochloride (XV).

A mixture of 4.84 g. (30 mmoles) of mesityl nitrile oxide (11), 3.34 g. (20 mmoles) of methyl 2,3-dehydroquinuclidine-3-carboxylate and 65 ml. of tetrahydrofuran was heated at reflux temperature for 20 hours in an apparatus fitted with a drying tube. The mixture was then concentrated and the residue was treated with ether. The ether solution was filtered and treated with anhydrous hydrogen chloride. This procedure gave 6.52 g. (89%) of methyl 3-[1-(2,4,6-trimethylphenyl)]isoxazol[2]ino[4,5-*b*]quinuclidine-7a-carboxylate hydrochloride (XV) as a white solid, m.p. 201-204°. An analytical sample, recrystallized two times from ethanol had m.p. 206-207.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_3\cdot HCl$ (364.86): C, 62.54; H, 6.91; N, 7.68; Cl, 9.72. Found: C, 62.80; H, 7.13; N, 7.48; Cl, 9.85.

Methyl 1,3-Diphenylpyrazol[2]ino[3,4-*b*]quinuclidine-3a-carboxylate Hydrochloride (XVI).

A mixture of 0.84 g. (5 mmoles) of methyl 2,3-dehydroquinuclidine-3-carboxylate (XIIIa) and 1.61 g. (7 mmoles) of *N*-(α-chlorobenzylidine)-*N'*-phenylhydrazine (16) in 25 ml. of purified tetrahydrofuran was chilled in an ice bath and treated with a solution of 0.81 g. (8 mmoles) of triethylamine in 10 ml. of tetrahydrofuran. After 16 hours at room temperature the mixture was filtered to remove triethylamine hydrochloride and the filtrate was concentrated. The residue was dissolved in ether and the filtered solution was treated with anhydrous hydrogen chloride. This procedure gave 1.23 g. (62%) of methyl 1,3-diphenylpyrazol[2]-ino[3,4-*b*]quinuclidine-3a-carboxylate hydrochloride (XVI) as pale yellow solid, m.p. 189-194°. An analytical sample, recrystallized two times from ethanol, had m.p. 223-225°.

Anal. Calcd. for $C_{22}H_{23}N_3O_2\cdot HCl$ (397.89): C, 66.41; H, 6.08; N, 10.56; Cl, 8.91. Found: C, 66.72; H, 6.18; N, 10.35; Cl, 9.09.

Acknowledgments.

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(4) Private communication from R. P. Williams, V. J. Bauer, and S. R. Safir.

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