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# Cardiovascular Activity of Some Substituted 2-Aminobenzoquinolizines


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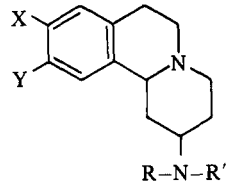
*Received April 17, 1971*


A series of substituted 2-aminobenzoquinolizines was synthesized and evaluated for antihypertensive and coronary dilator activity. Maximum antihypertensive activity was found in the trans isomer of *N*-phenyl-*N*-(1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)propionamide, which was selected for further evaluation.


In our search for novel antihypertensive compounds, we have synthesized a series of 2-aminobenzoquinolizines. The compounds chosen for study are illustrated by the general formula I where X and Y = H or methoxy; R = H, alkyl, aryl or aralkyl; R′ = H or acyl.




I

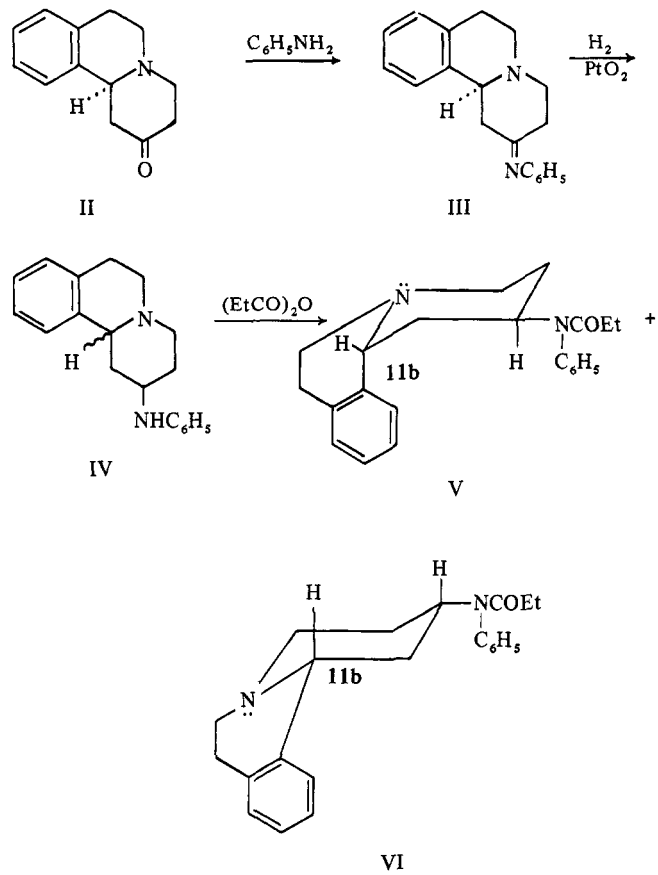
Compounds V (**1**, Table I) and VI (**2**, Table I) were originally prepared by treating 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (II)[1] with aniline to form the Schiff base III. The anil III was then hydrogenated with $PtO_2$ to give the amine IV which was propionylated to give the amides V (mp 157–158°) and VI (mp 126–127°)† in a ratio of approximately 1:2.

The proof that the amide V has the cis‡ configuration and the amide VI has the trans configuration can be obtained by examining the ir and nmr spectra. The ir spectrum of VI exhibits strong "Bohlmann bands"[2] at 2750 $cm^{-1}$ and 2800 $cm^{-1}$. These bands are characteristic for the trans isomer and are not present in the ir spectrum of the amide V.

The nmr spectra of these isomers indicated that the conformations assigned to them on the basis of their ir spectra were correct. Uskokovic, *et al.*,[3] have shown that the angular proton in a cis fused configuration in benzo[*a*]quinolizines is shifted to lower field (below δ 3.8). Nmr also allows one to distinguish between the two alternative cis forms (V and VII) by the splitting pattern of the angular proton. Since our compound shows a 1:2:1 triplet at δ 4.10 ($J$ = 4 cps) and not a 1:1:1:1 quartet, it was assigned conformation V. The nmr spectrum of VI showed no signal from δ 3.5 to 4.5.

Our findings are in complete agreement with those of Gootjes, *et al.*,[4] who have described in detail the stereochemistry of the benzoquinolizine system.

**Scheme I**




II III IV V

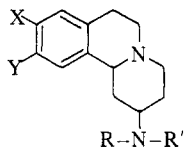



VI

†A crystalline modification melting at 134–135° can also be obtained.

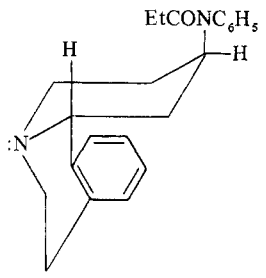
‡Cis and trans refer to the ring fusion.

**Table I**

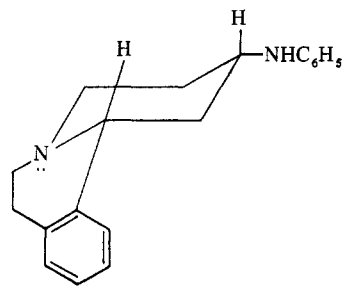


| Compd | X | Y | R | R′ | % yield[a] | Recrystn solvent | Mp, °C | Formula[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | $C_6H_5$ | $C_2H_5CO$ | 15.4 | $Et_2O$ | 157-158 | $C_{22}H_{26}N_2O$[c] |
| 2 | H | H | $C_6H_5$ | $C_2H_5CO$ | 46.5[d] | $Et_2O$ | 126-127 | $C_{22}H_{26}N_2O$ |
| 3 | H | H | $C_6H_5$ | H | 58.1 | Sk B | 104-105 | $C_{19}H_{22}N_2$ |
| 4 | H | H | $C_6H_5(CH_2)_2$ | H | 61.5 | MeOH-EtOAc | 326-329 | $C_{21}H_{26}N_2 \cdot 2HCl$ |
| 5 | H | H | $C_6H_5(CH_2)_2$ | $C_2H_5CO$ | 75.5 | EtOAc-*i*-PrOH | 199-202 | $C_{24}H_{30}N_2O \cdot HCl$ |
| 6 | H | H | $C_6H_5CH_2$ | H | 50.9 | EtOH-EtOAc | 280-281 | $C_{20}H_{24}N_2 \cdot 2HCl$ |
| 7 | H | H | $C_6H_5CH_2$ | $C_2H_5CO$ | 42.4 | EtOH-EtOAc | 194-196 | $C_{23}H_{28}N_2O \cdot HCl$ |
| 8 | H | H | $CH_3$ | H | 45.2 | EtOH-EtOAc | 305-310 | $C_{14}H_{20}N_2 \cdot 2HCl$ |
| 9 | H | H | *cyclo*-$C_6H_{11}$ | H | 48.1 | MeOH-*i*-PrOH | 319-321 | $C_{19}H_{28}N_2 \cdot 2HCl$ |
| 10 | H | H | *cyclo*-$C_6H_{11}$ | $C_2H_5CO$ | 25.0 | MeOH | 216-225 | $C_{22}H_{32}N_2O \cdot HCl$ |
| 11 | H | H | 2,4-$(CH_3O)_2C_6H_3$ | H | 54.4 | MeOH | 116-118 | $C_{21}H_{26}N_2O_2$ |
| 12 | H | H | 2,4-$(CH_3O)_2C_6H_3$ | $C_2H_5CO$ | 41.9 | MeOH-$Et_2O$ | 265-267 | $C_{24}H_{30}N_2O_3 \cdot HCl$ |
| 13 | H | H | 3,4,5-$(CH_3O)_3C_6H_2$ | H | 17.5 | MeOH | 225-228 | $C_{22}H_{28}N_2O_3 \cdot 2HCl$[e] |
| 14 | H | H | 3,4,5-$(CH_3O)_3C_6H_2$ | $C_2H_5CO$ | 23.4 | *i*-PrOH-$Et_2O$ | 197.5-198 | $C_{25}H_{32}N_2O_4 \cdot HCl$ |
| 15 | H | H | 3,4-$Cl_2C_6H_3$ | H | 28.2 | MeOH | 209-212 | $C_{19}H_{20}Cl_2N_2 \cdot 2HCl \cdot MeOH$ |
| 16 | H | H | 3-$CH_3C_6H_4$ | H | 18.0 | EtOH | 256-266 | $C_{20}H_{24}N_2 \cdot 2HCl$ |
| 17 | H | H | 4-$C_6H_5C_6H_4$ | H | 25.6 | MeOH | 258-268 | $C_{25}H_{26}N_2 \cdot 2HCl$ |
| 18 | H | H | 4-$CNC_6H_4$ | H | 19.7 | *i*-PrOH | 185 dec | $C_{20}H_{21}N_3 \cdot HCl \cdot$ *i*-PrOH |
| 19 | H | H | 3-$NO_2C_6H_4$ | H | 16.1 | *i*-PrOH | 211-216 dec | $C_{19}H_{21}N_3O_2 \cdot 2HCl$ |
| 20 | H | H | 4-$C_2H_5O_2CC_6H_4$ | H | 6.50 | MeOH | 271-276 dec | $C_{22}H_{26}N_2O_2 \cdot HCl$ |
| 21 | H | H | 4-$CH_3C_6H_4$ | H | 6.90 | EtOH | 273 dec | $C_{20}H_{24}N_2 \cdot HCl \cdot H_2O$ |
| 22 | H | H | H | H | 30.0 | EtOH | 164-166 dec | $C_{13}H_{18}N_2 \cdot 2(C_4H_4O_4)$[f] |
| 23 | $CH_3O$ | $CH_3O$ | $C_6H_5$ | $C_2H_5CO$ | 18.5 | *i*-PrOH-$Et_2O$ | 247-249 dec | $C_{24}H_{30}N_2O_3 \cdot HCl$ |
| 24 | H | H | 3-$CH_3C_6H_4$ | $C_2H_5CO$ | 18.2 | EtOH-EtOAc | 192-198 | $C_{23}H_{28}N_2O \cdot HCl$ |
| 25 | H | H | 4-$CNC_6H_4$ | $C_2H_5CO$ | 7.00 | *i*-PrOH-EtOAc | 348-358 dec | $C_{23}H_{25}N_3O \cdot HCl$ |
| 26 | H | H | 4-$C_6H_5C_6H_4$ | $C_2H_5CO$ | 9.50 | MeOH-EtOAc | 274-279 dec | $C_{28}H_{30}N_2O \cdot HCl$ |
| 27 | H | H | $C_6H_5$ | $CH_3CO$ | 33.6 | *i*-PrOH-EtOAc | 253-259 | $C_{21}H_{24}N_2O \cdot HCl$ |
| 28 | H | H | $C_6H_5$ | $C_3H_7CO$ | 41.2 | MeOH-EtOAc | 163-168 | $C_{23}H_{28}N_2O \cdot HCl \cdot MeOH$ |
| 29 | H | H | $C_6H_5$ | $C_6H_5CO$ | 26.6 | MeOH-EtOAc | 175-176.5 | $C_{26}H_{26}N_2O \cdot HCl \cdot MeOH$ |
| 30 | H | H | $C_6H_5$ | ▷—CO | 54.9 | MeOH-EtOAc | 194-195 | $C_{23}H_{26}N_2O \cdot HCl \cdot MeOH$ |
| 31 | H | H | H | $C_2H_5CO$ | 6.80 | *i*-PrOH | 200 dec | $C_{18}H_{22}N_2O \cdot HCl$ |
| 32 | H | H | 3-$NO_2C_6H_4$ | $C_2H_5CO$ | 1.20 | *i*-PrOH-$Et_2O$ | 160-161 | $C_{22}H_{25}N_3O_3 \cdot HCl$ |
| 33 | H | H | 3,4-$Cl_2C_6H_3$ | $C_2H_5CO$ | 2.30 | DMF-EtOAc | 175-180 | $C_{22}H_{24}Cl_2N_2O \cdot HCl$ |
| 34 | H | H | 4-$CH_3C_6H_4$ | $C_2H_5CO$ | 10.9 | EtOH-EtOAc | 258-266 dec | $C_{23}H_{28}N_2O \cdot HCl$ |
| 35 | H | H | 3-$C_2H_5O_2CC_6H_4$ | $C_2H_5CO$ | 3.40 | $CHCl_3$-$Et_2O$ | 147 dec | $C_{25}H_{30}N_2O_3 \cdot HCl$[g] |
| 36 | H | H | 4-$CH_3OC_6H_4$ | H | 17.1 | MeOH | 262-265 dec | $C_{20}H_{24}N_2O \cdot 2HCl$ |
| 37 | H | H | 3-$C_2H_5O_2CC_6H_4$ | H | 2.60 | MeOH | 241.5-244 | $C_{22}H_{26}N_2O_2 \cdot 2HCl$ |
| 38 | H | H | 3-$CH_3C_6H_4$ | $CH_3CO$ | 1.35 | $CHCl_3$-$Et_2O$ | 221-226 | $C_{22}H_{26}N_2O \cdot HCl$ |

[a] Yield calcd from starting 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2-one. [b] All compds were analyzed for C, H, N and the anal. values were within ±0.4 of the calcd figures, unless indicated otherwise. [c] Cis isomer. [d] Yield obtd from catalytic reduction was 14.4%. [e] C: Calcd, 59.86; found, 59.22. [f] Dimaleate. [g] C: Calcd, 67.78; found, 66.33.



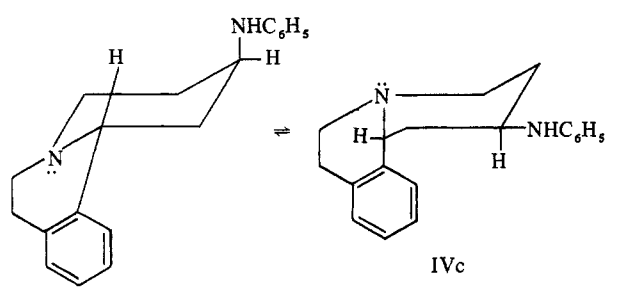
VII



IVa

When the trans Schiff base III is hydrogenated with $PtO_2$, attack occurs from both sides giving IVa (**3**, Table I) and IVb. The isomer IVa should be a stable conformation since there are no large axial groups. Isomer IVb, on the other hand, has a bulky axial anilino group. Due to the stereochemical instability of the tertiary N,[4] IVb can rearrange to the cis isomer IVc wherein the anilino group and the angular proton are in equatorial conformations.

Since the cis isomer V (**1**, Table I) was devoid of any antihypertensive activity, a method was needed for obtaining



IVb ⇌ IVc

**Table II.** Hypotensive and Coronary Dilator Activity

| Compound | Hypotension | Coronary dilatation | Compound | Hypotension | Coronary dilatation |
|---|---|---|---|---|---|
| **1** | 0 | 0 | **20** | 0 | 0 |
| **2** | + | 0 | **21** | 0 | 0 |
| **3** | + | + | **22** | + | 0 |
| **4** | 0 | 0 | **23** | 0 | 0 |
| **5** | + | 0 | **24** | 0 | 0 |
| **6** | 0 | 0 | **25** | 0 | 0 |
| **7** | 0 | + | **26** | 0 | 0 |
| **8** | + | + | **27** | 0 | 0 |
| **9** | 0 | 0 | **28** | 0 | 0 |
| **10** | + | + | **29** | 0 | 0 |
| **11** | + | 0 | **30** | 0 | 0 |
| **12** | + | 0 | **31** | 0 | 0 |
| **13** | 0 | + | **32** | 0 | + |
| **14** | + | 0 | **33** | 0 | 0 |
| **15** | 0 | 0 | **34** | 0 | 0 |
| **16** | + | 0 | **35** | 0 | 0 |
| **17** | 0 | 0 | **36** | + | + |
| **18** | 0 | 0 | **37** | 0 | 0 |
| **19** | 0 | + | **38** | + | 0 |

**Table III.** Chronic Antihypertensive Activity in Mecamylamine Hypertensive Dogs

| Compound | Δ mean blood pressure, mm | Compound | Δ mean blood pressure, mm |
|---|---|---|---|
| **2** | −22 | **12** | −23 |
| **3** | −32 | **14** | − 9 |
| **5** | −11 | **16** | −21 |
| **8** | − 4 | **22** | − 9 |
| **10** | −25 | **36** | − 3 |
| **11** | + 6 | **38** | + 2 |

the trans isomer in larger proportion. It was found that reduction of the Schiff base III with $NaBH_4$, gives almost exclusively the more stable equatorial amine IVa.[5] This amine was then propionylated to give the amide VI with very little V being detected.

The other amines in Table I were prepared by $NaBH_4$ reduction of the Schiff base except for the primary amine **22** which was prepared by reducing 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one oxime[1] with LAH. The amine **8** was prepared by heating the ketone II with anhyd $MeNH_2$ under pressure followed by $NaBH_4$ reduction.

The amides were prepared by treating the amines with the appropriate anhydride except for **29** and **30**. These amides were prepared by treating the amine with BzCl and cyclopropanecarbonyl chloride, respectively.

**Pharmacology.** Acute hypotensive activity was determined in male cats anesthetized with a mixture of pentobarbital-barbital. Blood pressure was recorded continuously from a cannulated femoral artery before and for 2 hr after iv administration of 0.03 mmoles/kg of the test drugs. Compounds producing a mean blood pressure decrease of more than 15% during the total observation period, were considered active and were tested for chronic antihypertensive effects in dogs with mecamylamine-induced hypertension.[6] In these animals, compounds were administered for 4 weeks at an oral dose of 3.1 mg/kg per day, and blood pressure values during this period compared with those observed during the previous month. Compounds **2**, **3**, **5**, **8**, **10**, **11**, **12**, **14**, **16**, **22**, **36**, and **38** produced acute, long-lasting hypotension in the anesthetized cat, but of these, only **2**, **3**, **10**, **12**, and **16** effectively reduced the blood pressure of hypertensive dogs upon repeated administration (mean blood pressure fall 20 mm). Compound **2** was selected for further evaluation; detailed general pharmacological and cardiovascular studies, to be published elsewhere, indicate that its actions can be attributed to peripheral vasodilation.

Coronary dilator activity was assessed in pentobarbital-anesthetized, open-chest dogs in which left coronary flow, aortic blood pressure, and heart rate were measured with an electromagnetic flowmeter, a pressure transducer, and a tacograph, respectively. Coronary resistance was calcd by dividing mean blood pressure by flow. Compounds were administered iv at a dose of 1.0 mg/kg. Coronary vasodilation was considered to be present if resistance was decreased by at least 30% for more than 10 min, with heart rate remaining within 15% of control values.

## Experimental Section§

***N*-Phenyl-*N*-(1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)propionamide.** 1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-one (354 g, 1.76 moles), aniline (180 g, 1.94 moles), and *p*-TsOH (1 g) in 2 l. of PhMe were heated to reflux for 16–20 hr while collecting the $H_2O$ of reaction in a Dean–Stark trap. The solvent was distd on a steam bath *in vacuo*. The residue was recrystd from *i*-PrOH to give 379 g of 2-phenylimino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine, mp 131–133°.

A 49.5-g sample of this imine was hydrogenated in MeOH using $PtO_2$ for 1.5 hr. The mixt was filtered, and the solvent was evapd *in vacuo*. $(EtCO)_2O$ (200 ml) was added to the residue, and the soln was heated to reflux for 6 hr. The reaction mixt was evapd on a steam bath *in vacuo*. $H_2O$ was added to the semisolid residue and warmed on a steam bath. The insol portion was removed by filtration, and the filtrate was made basic with $K_2CO_3$. The semisolid ppt that formed soon solidified and was collected by filtration and washed with $H_2O$. The ppt was dissolved in $CHCl_3$, dried ($MgSO_4$), and stripped of $CHCl_3$ *in vacuo*. The residue was stirred with cold $Et_2O$ and the solid filtered to give 14 g (crop 1). The $H_2O$-insol portion was dissolved in dil HCl, and the free base was pptd with $K_2CO_3$. The ppt was dissolved in $CHCl_3$, dried ($MgSO_4$), and stripped of $CHCl_3$ *in vacuo*. The residue was stirred with cold $Et_2O$ and the solid filtered to give 29 g (crop 2).

**Cis Isomer (1).** The solid (crop 1) which was almost pure cis isomer was recrystd from $C_6H_6$–Skelly B, yield 8.5 g, mp 157–158°. An addl 3.3 g of pure cis isomer was obtd from a chromatog of crop 2 and crop 1 filtrate which is described under trans isomer.

**Trans Isomer (2).** Crop 2 was a mixt of cis and trans isomers. It was combined with the filtrate from the recrystn of crop 1 and chromatogd on neutral $Al_2O_3$ Brockman activity I (Fisher). The trans isomer (12 g) was obtd by eluting with $C_6H_6$ or $C_6H_6$–$Et_2O$ (4:1). It was recrystd from $Et_2O$, yield 11 g, mp 125–126°. A mixt of cis and trans isomers (3.9 g) was obtd by eluting with $C_6H_6$–$Et_2O$ (1:1). Addl cis isomer (3.3 g) was obtd by eluting with $Et_2O$ and then recrystg once from $C_6H_6$–Skelly B and once from $Et_2O$.

**2-Benzylamino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Dihydrochloride (6).** 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (40.2 g, 0.2 mole) was dissolved in 450 ml of dry $C_6H_6$. Benzylamine (21.4 g, 0.2 mole) was added to the above soln along with a catalytic amt of *p*-TsOH, and the soln was heated to reflux for 3 hr using a Dean-Stark trap to remove 3.6 ml of $H_2O$. The soln was cooled and concd *in vacuo* to a syrup, ir ($CHCl_3$) 1670 $cm^{-1}$ (C=N). The syrup was then dissolved in 200 ml of MeOH and cooled in an ice bath. $NaBH_4$ (16 g, 0.42 mole) was added in small portions with stirring to the cold MeOH soln. After the bubbling had ceased, the resulting soln was heated to reflux for 1 hr and then concd *in vacuo* to a vol of 200 ml. $H_2O$ (300 ml) was slowly added followed by the addn of 300 ml of $Et_2O$. The resulting 2-phase system was transferred to a separatory funnel and the aq layer was then extd with $Et_2O$. The combined $Et_2O$ exts were dried ($MgSO_4$) and filtered. The filtrate was concd *in vacuo* to a syrup (57.2 g). A 10-g sample of the syrup was dissolved in 200 ml of *i*-PrOH and then a soln of HCl in *i*-PrOH was slowly added until the soln was strongly acidic. The soln was concd to 200 ml by boiling on a hot plate and EtOAc was added until a white solid began to ppt. The white solid which formed upon cooling was recrystd from EtOH–EtOAc to give 6.5 g of material melting at 280–281° dec.

All the other amines were similarly prepd and are recorded in Table I.

§ All mps are uncor and were detd with a Büchi capillary mp app (W. Büchi, Glasapparatefabrik, Flawil, Switzerland). Ir spectra were detd with a Perkin-Elmer Model 237 grating spectrophotometer. Where analyses are indicated by symbols, the elements or functions were within ±0.4% of the calcd values.

*N*-**Benzyl-*N*-(1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)propionamide Hydrochloride (7).** Compd **6** (10 g, 0.034 mole) was dissolved in 150 ml of $C_6H_6$. To the resulting soln was added $(EtCO)_2O$ (4.5 g, 0.035 mole), and an initial rise in temp of 5° was noted. The soln was heated to reflux for 2 hr, then cooled, and extd 3 times with aq $Na_2CO_3$. The $C_6H_6$ layer was dried ($MgSO_4$) and filtered. The filtrate was concd *in vacuo* to a syrup (13.0 g), ir ($CHCl_3$) 1630 $cm^{-1}$ (NHC=O). The hydrochloride was formed by dissol of the syrup in $Et_2O$ followed by bubbling through gaseous HCl. The white solid which formed was removed by filtration and was recrystd from anhyd EtOH–EtOAc to yield 5.7 g, mp 194–196°.

All the other propionamides and acetamides were prepd similarly and are recorded in Table I.

*N*-**Phenyl-*N*-(1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)benzamide Monohydrochloride Monomethanolate (29).** BzCl (7 ml, 0.06 mole) was added dropwise to a stirred, refluxing soln of 2-anilino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (13.9 g, 0.05 mole), 100 ml of dry THF, and 25 ml of dry pyridine. The resulting soln was heated to reflux for 12 hr and then poured over ice. A white solid formed, and 20% NaOH was added to decomp any excess BzCl. The mixt was extd with $Et_2O$ and the combined $Et_2O$ exts were dried ($MgSO_4$) and filtered. The filtrate was concd *in vacuo*. The residue was recrystd from a mixt of $C_6H_6$ and Skelly C to yield 11.1 g of white solid, mp 113–115°. The product was dissolved in warm MeOH and 11 ml of 2.7 *N* HCl in *i*-PrOH was added. A ppt formed which was filtered and recrystd from MeOH–EtOAc to give 10.3 g of white solid melting at 175–176.5°.

Compd **30** was similarly prepd.

**2-Methylamino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Dihydrochloride (8).** 1,3,4,6,7,11b-Hexahydro-2*H*-benzo-[*a*]quinolizin-2-one (40.2 g, 0.20 mole) and a catalytic amt of *p*-TsOH was dissolved in 300 ml of anhyd EtOH. Anhyd $MeNH_2$ was bubbled through the soln until it was satd. The soln was then heated at 65° at a pressure of 3.5 $kg/cm^2$ for 8 hr. The soln was concd to a syrup *in vacuo*, ir ($CHCl_3$) 1670 $cm^{-1}$ (C=N). The syrup was then dissolved in 300 ml of MeOH and cooled in an ice bath. $NaBH_4$ (16.0 g, 0.42 mole) was added in small portions with stirring. After the bubbling had ceased the soln was heated to reflux for 1.5 hr. The solvent was removed *in vacuo* to yield a syrup. The syrup was shaken with 1:1 $H_2O$–$Et_2O$ (400 ml). The resulting 2 phases were sepd and the aq phase was extd with $Et_2O$. The combined $Et_2O$ exts were dried ($MgSO_4$) and then filtered. The filtrate was concd *in vacuo* to a syrup, yield 46.2 g. A 20-g sample of the syrup was dissolved in anhyd $Et_2O$ (1000 ml) and gaseous HCl was bubbled through the stirred soln. The white ppt which formed was removed by filtration and recrystd from anhyd EtOH–EtOAc to yield 6.0 g, mp 305–310°.

**1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-one Oxime.** A mixt of 1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-one (20.1 g, 0.10 mole), $NH_2OH \cdot HCl$ (20.1 g, 0.289 mole), 100 ml of pyridine, and 100 ml of anhyd EtOH was heated to reflux on a steam bath for 2.5 hr. The solvent was removed *in vacuo*, and the residue was triturated with 100 ml of cold $H_2O$ and then filtered to yield 31 g, mp 254°. The product was dissolved in 1500 ml of hot $H_2O$, and the soln was cooled in an ice bath. The cold soln was made alk with $NaHCO_3$ and the resulting ppt was recrystd from $C_6H_6$–Skelly C to yield 16.2 g, mp 160–165°, lit.[1] mp 182–183°.

**2-Amino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Dimaleate (22).** A soln of 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizin-2-one oxime (15.0 g, 0.069 mole) in 275 ml of dry THF was added dropwise with stirring to a suspension of LAH (7.8 g, 0.21 mole) in 300 ml of dry THF. The reaction mixt was heated to reflux for 25 hr. The redn complex and excess LAH were decompd by the successive dropwise addn of 7.8 ml of $H_2O$ in 78 ml of THF, 5.85 ml of 20% NaOH, and 27.3 ml of $H_2O$ to the stirred cold reaction mixt. The resulting mixt was stirred in an ice bath for 2 hr, then filtered, and washed with THF. The filtrate was concd *in vacuo* to an oil which was dissolved in $CHCl_3$, dried ($MgSO_4$), and then filtered. The filtrate was concd *in vacuo* to a yellow oil. Sufficient anhyd EtOH was added to the yellow oil to effect dissolution at room temp. To the resulting soln was added maleic acid (15.4 g, 0.14 mole) in anhyd EtOH. The ppt which formed upon cooling was removed by filtration and washed with cold anhyd EtOH. Recrystn from EtOH gave 12.0 g, mp 164–166°.

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# *Notes*

## *N*-Carbalkoxy-*O*-alkylalkanamidoximes. A New Series of Insecticides


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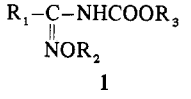
*Received June 25, 1971*

Aryl N-substituted carbamates are useful in the control of a variety of pests. Simple alkyl carbamates showing insecticidal activity have not been described, however. Of the commercially useful aryl carbamates those bearing an *N*-Me substituent show a broader spectrum of activity than the corresponding *N,N*-$Me_2$ derivatives.[1]

A new series of carbamate derivatives, *N*-carbalkoxy-*O*-alkylalkanamidoximes, 1, show activity though they are alkyl rather than aryl carbamates and bear a large substituent on N.



1

The new compounds were prepared from 2-alkoxyiminocarboxamides by a modification of the Hofmann hypobromite reaction[2] (Table I). The 2-alkoxyiminoamides were prepared by established procedures.[3] With the exception of 2-ethoxyiminobutanamide and 2-ethoxyiminopropanamide the amides have been reported previously.[3]

**Biological Data.** Test organisms used in the insecticidal screen are the blowfly [*Calliphora vicina* Robineau-Descoidy], the fruit fly [*Drosophila melanogaster* Meigen], German cockroach [*Blattella germanica* (L.)], yellow mealworm [*Tenebrio molitor* (L.)], saw-toothed grain beetle [*Oryzaephilus surinamensis* (L.)], and the varied carpet beetle [*Anthrenus verbasci* (L.)].

In the test, circles of filter paper (9-cm diam) were sprayed with 2.5 ml of a 5% $Et_2O$ soln of the test compd. The filter paper was air-dried for 1 hr, placed in a covered petri dish

†M. S. Thesis, University of Illinois at the Medical Center, 1966.