Antimalarials. 5. α-Dibutylaminomethyl- and α-(2-Piperidyl)-3-quinolinemethanols[1]

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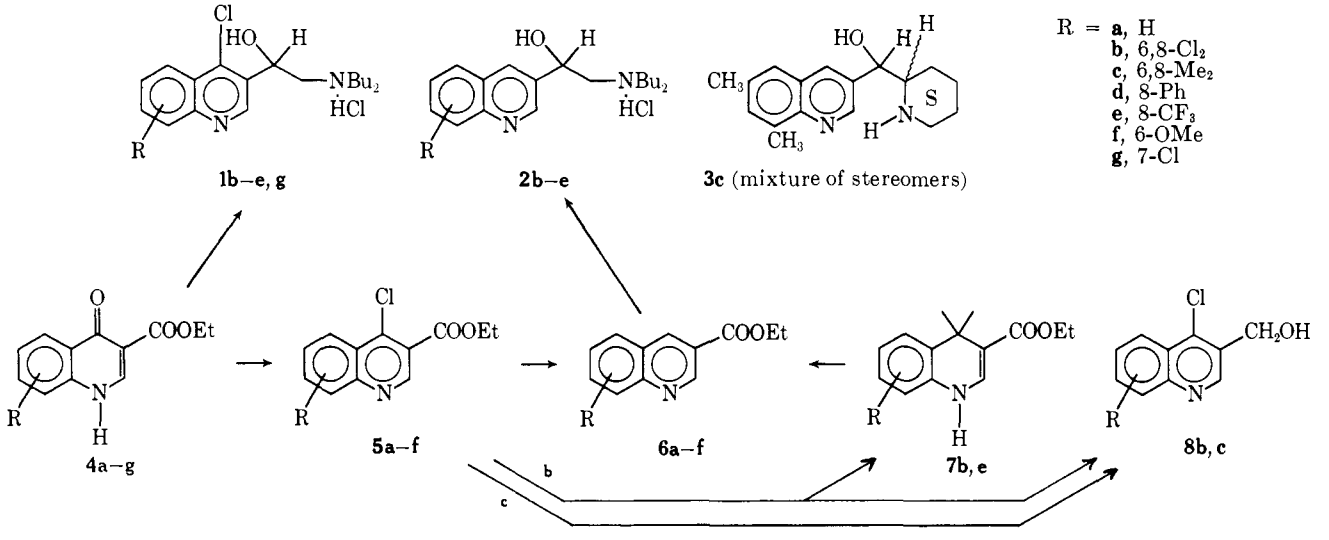
Eight α-dialkylaminomethyl-3-quinolinemethanols without 2 substituents were synthesized from 4-quinolone-3-carboxylic esters, by conversions into the 4-chloro esters and reductive 4-dechlorinations, and thence through the acids, diazomethyl ketones, and epoxides. Attempts to prepare α-(2-piperidyl) analogs involved complications due to nuclear additions of 2-pyridyllithium and nonselectivity in hydrogenations of the pyridyl ketones. One example, α-(2-piperidyl)-6,8-dimethyl-3-quinolinemethanol, fortuitously, was produced by Pt–H_2 on 4-chloro-6,8-dimethyl-3-quinolyl 2-pyridyl ketone (a diasteroisomeric mixture). These 3-amino alcohols were inactive against *Plasmodium berghei* in mice.

In continuation of the search for improved antimalarials, eight new α-aminoalkyl-3-quinolinemethanols without 2 substitutents,[1b] **1–3**, have been synthesized under the program of moving the amino alcohol group away from the 4 location in quinine and its many synthetic analogs. The hope was to find active drugs with a minimum of the phototoxicity so common to the 2-aryl-4-amino alcohols. As features of possible significance, these compounds lack the quasiconjugation of the amino alcohol group with the quinoline nuclear C=N–C system which is involved in the 4-quinoline amino alcohol series, and they have two rather than three nuclear carbons intervening between the quinoline N and the amino alcohol group.



The starting materials for these synthesis were the 4-quinolone-3-carboxylic esters **4a–g** which were easily obtainable by condensation of the appropriate aniline with ethoxymethylenemalonate ester.[3] Six 4-chloro esters **5a–f** were made from these by the action of $POCl_3$.

Reductive 4-dechlorinations of **5** to **6** were accomplished by variations of previously reported hydrogenolyses, using Pd–C[4] or Raney Ni[5] as catalyst. In four cases, **5a**, **c**, **d**, and **f**, the dechlorinations proceeded well using 10% Pd–C in glacial AcOH at 50°. However, **5e** under these conditions gave low and nonreproducible yields of **6e** along with an overreduction product, the 1,4-dihydroquinoline **7e**; and when the Pd–C reduction was carried out in ethanolic KOH at 50° the dihydroquinoline **7e** became the chief product (61%). This dihydro compound **7e** in a second step underwent S dehydrogenation in good yield to the desired 3-carbethoxyquinoline **6e**.

Attempted Pd–C and Raney Ni 4-monodehalogenation of the 4,6,8-trichloro derivative **5b** was unsuccessful. However, $NaBH^4$ reduction of **5b** in cold 2-methoxyethanol gave the dihydro-4-dehalogenated ester **7b** (39%) along with 4,6,8-trichloro-3-quinolinemethanol (**8b**), a result consistent with published observations.[4,6]

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(2) (a) Postdoctoral Research Assistant; (b) M. S. Thesis, University of Virginia, 1969; (c) preliminary work toward starting materials was done by D. P. Clifford and A. R. Patel, Postdoctoral Research Assistants.

(3) (a) C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204 (1946); (b) J. H. Wilkinson, *J. Chem. Soc.*, 464 (1950); (c) B. Riegel, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1264 (1946).

(4) C. E. Kaslow and W. R. Clark, *J. Org. Chem* **18**, 55(1953).

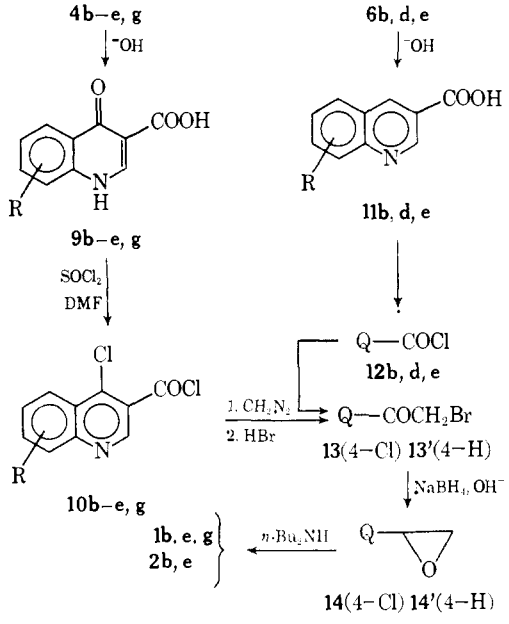
(5) (a) R. E. Lutz, G. Ashburn, and R. J. Rowlett, Jr., *J. Amer. Chem. Soc.*, **68**, 1322 (1946); (b) A. S. Day and M. M. Joullié, *J. Heterocycl. Chem.*, **2**, 113 (1965); (c) K. N. Campbell, *et al.*, *J. Org. Cehm.*, **11**, 403 (1946).

(6) (a) G. N. Walker and B. N. Weaver, *ibid.*, **25**, 484 (1960); (b) M. S. Brown and H. Rapoport, *ibid.*, **28**, 3261 (1963).

Subsequent S dehydrogenation of **7b** gave the desired quinoline **6b** (92%).

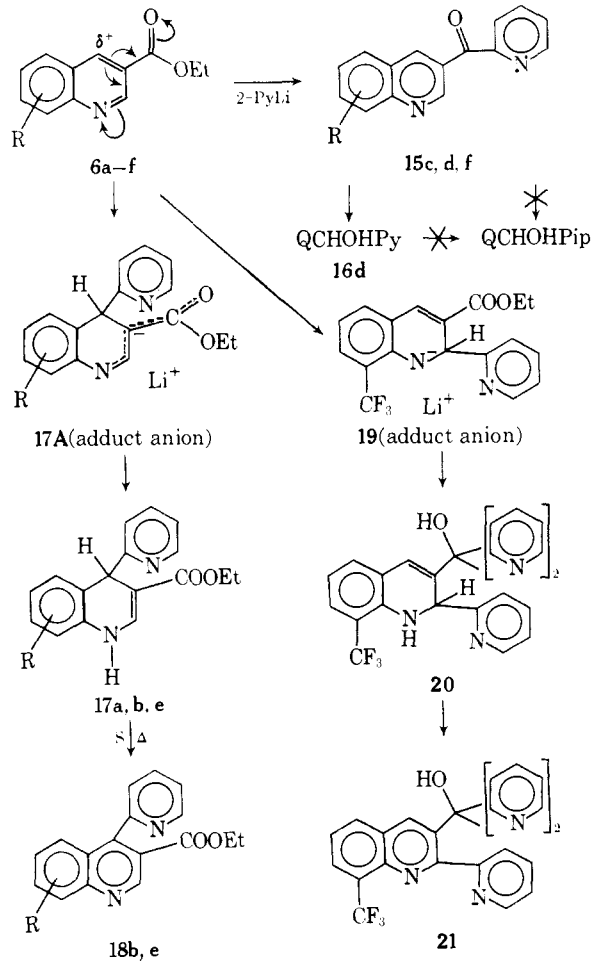
Interestingly, $NaBH^4$ in 2-methoxyethanol did not dehalogenate 6,8-dimethyl-4-chloro-3-carbethoxyquinoline but instead brought about reduction of the 3-carbethoxy group to the methanol **8c** (53%).

α-Di-*n*-butylaminomethyl-3-quinolinemethanols.—Seven of these, **1b–e, g**, and **2b, e**, were prepared by adaptations of the standard scheme.[7] The 3-carbethoxy-4-quinolones and quinolines **4b–e, g** and **6b, d, e** were converted into the acids **9b–e, g** and **11b, d, e** and then by $SOCl_2$ into the acid chlorides **10b–e, g** and **12b, d, e**. DMF was required as catalyst in the latter reaction with the quinolones. Diazomethylations of the acid chlorides followed by hydrobromination without isolation of the diazoketones gave the bromo ketones **13** and **13′**. These were converted into the epoxides **14** and **14′** by $NaBH^4$ reduction and dehydrohalogenation of the resulting bromohydrins by accompanying or subsequently added base. Condensation of the epoxides with *n*-Bu_2NH gave the target amino alcohols **1b–e, g** and **2b, e**.



α-(2-Piperidyl)-3-quinolinemethanols (3).—The Boykin procedure for the preparation of α-(2-pyridyl)-3-quinolyl ketones from 3-quinolinecarboxylic acids, by addition of 2-pyridyllithium followed by selective catalytic reduction of the pyridyl ring,[8] was not generally successful. Two of the acids without a substitutent in the 4 position, **11d** and **11e**, gave only low yields of the desired 2-pyridyl ketones **15d** and **e**.

The addition of 2-pyridyllithium to 3-carboxylic esters was therefore investigated with interesting results of limited usefulness. To a significant extent addition occurred at the carbethoxy group of the 6,8-dimethyl, 8-phenyl, and 6-methoxy esters **6c, d, f**, giving 2-pyridyl ketones **15c, d, f**, (15, 66, and 66%, respectively). On the other hand, the reactions with the parent ester and the 6,8-dichloro and 8-trifluoromethyl analogs, **6a, b, e**, gave the 4-(2-pyridyl)-1,4-dihydro-3-carbethoxyquinolines **17a, b, e** in yields of 0.7, 18, and 20%, respectively. The structures **17** were assigned on the basis of elemental analyses, ir and nmr spectra, and S dehydrogenation of two of them (**17b,e**) to the 4-pyridyl-3-carbethoxyquinolines **18b,e**. The nmr spectra of the latter, **18b, e**, showed characteristic quinoline H-2



protons as sharp singlets at δ 9.58 and 9.46, respectively, which were assignable as such on the basis of the known chemical shifts of δ 9.36 ± 0.02 for the H-2 protons of 4-phenyl-3-carbethoxyquinolines[9] and the distinctively upfield chemical shifts for the H-4 protons of 2-substituted quinolines.[10] Only in the reaction of **6e** was a second product isolated (11%), which appears to be the result of addition of pyridyllithium to the quinoline nucleus, and to which the structure **20**, α-bis(2-pyridyl)-2-(2-pyridyl)-1,2-dihydro-8-trifluoromethyl-3-quinolinemethanol, is tentatively assigned on the basis of elemental analysis, ir, nmr, and mass spectra, and S dehydrogenation to **21** where the nmr spectrum revealed a quinoline H-4 proton at δ 7.59 (see Experimental Section for comparison with nmr of **3c**) and no H-2 proton. In the above and presumably reversible Michael type addition of pyridyllithium to the crossconjugated system of **6** at the highly δ^+ C-4, the expected or necessary adduct anion **17A** would be considerably stablized by resonance involving the ester CO and would resist further attack at the ester function. On the other hand ad-

(7) R. E. Lutz *et. al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).

(8) (a) D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967); (b) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968).

(9) N. D. Heindel, P. D. Kennwell, and C. J. Ohnmacht, *J. Org. Chem.*, **34**, 1168 (1969).

(10) Japan Electron Optics Laboratory Co. Ltd., "JOEL High Resolution NMR Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967.

dition at C-2 would yield intermediate anion **19** in which the ester function is conjugatively free for further reaction. Literature analogies for these reactions are seen in the addition of $PhCH_2MgBr$[11] and BuLi[12] to C-2 and C-4 of quinoline itself. The often low material balance in the PhLi additions is evident from Table I where

TABLE I

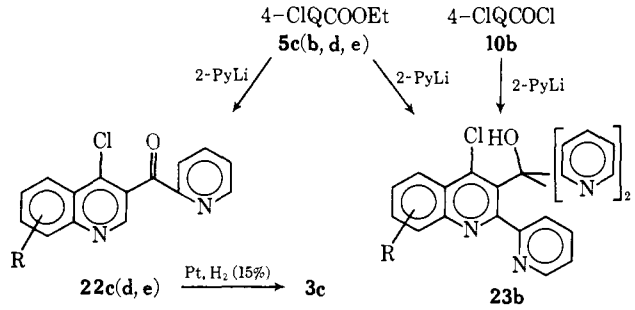
CHEMICAL SHIFTS OF H-2 AND H-4 OF SUBSTITUTED 3-CARBETHOXYQUINOLINES **6**

	R	Products (%)	H-2 δ	H-4 δ
6c	6,8-Me_2	**15c** (15)	9.50	8.42
f	6-OCH_3	**15f** (66)	9.38	8.73
b	6,8-Cl_2	**16b** (18)	9.51	8.74
e	8-CF_4	**16e** (20), **20** (11)	9.61	8.89
a	H	**16a** (0.8)	9.55	8.90
d	8-Ph	**15d** (66)	9.55	8.90

yields of products are compared with the H-2 and H-4 nmr chemical shifts which are a measure of substituent electronic effects on the two possible sites of initial nuclear attack. The seemingly anomolous behavior of the 8-Ph analog **6d** in respect to prediction based solely on its H-4 nmr chemical shift might be explained in terms of steric hindrance at the quinoline N toward coordination with 2-pyridyllithium.[13]

Unfortunately attempts to hydrogenate selectively the 2-pyridyl nucleus of either pyridyl ketones **15c, d, f** or α-(2-pyridyl)-8-phenyl-3-quinolinemethanol (obtained through $NaBH_4$ reduction of **15d**) yielded dark mixtures which were shown by tlc to be multicomponent. These results are in contrast to the usually successful reductions of the pyridyl rings of the 2-aryl types[8] where the 2 substitutent appears to permit these selective reductions, probably by sterically decreasing the facility of reduction of the N-containing ring of the quinoline nucleus.

The successful and fortuitious synthesis of one example of the desired α-(2-piperidyl)-6,8-dimethyl-3-quinolinemethanol (**3c**), stemmed from the work described below which was designed to obtain target analogs carrying Cl or some other heteroelemental group at position 4. This synthesis proceeded through the quinolone ester **4c** and the 4-chloro-(2-pyridyl) ketone **22c**. This ketone **22c** was unique in undergoing selective hydrogenation of the pyridyl nucleus with simultaneous reductive 4-dechlorination. This uniqueness possibly may be due to a combination of electronic stabilization by the electron-repelling Me groups and a steric effect of the 8-Me not unlike that of a 2-aryl group.

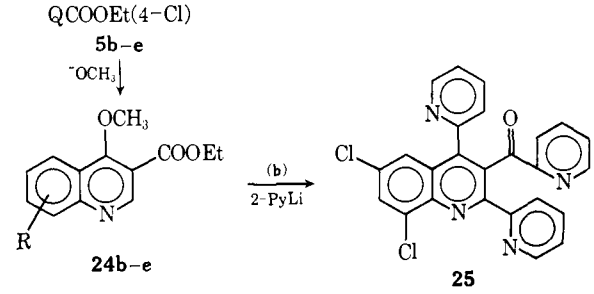


(11) E. Bergmann and W. Rosenthal, *J. Prakt. Chem.*, **135**, 267 (1932).
(12) K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).
(13) (a) A. Kaufmann, P. Dändliker and H. Burkhardt, *Ber.*, **46**, 2929 (1913); (b) J. B. Wommack, T. G. Barbee, Jr., D. J. Tholness, M. A. McDonald and D. E. Pearson, *J. Heterocycl. Chem.*, **6**, 245 (1969).

The target amino alcohol **3c** was shown actually to be a mixture of difficultly separable diastereomers. This fact had not been revealed by tlc and became evident from the nmr spectrum of analytical samples which showed a pair of carbinol α-proton doublets of δ 4.56 (J = 8 Hz) and 4.85 (J = 5 Hz) in an integration ratio of 59:41 with total integration for one H^+. Work on this problem has not been undertaken because of the lack of significant antimalarial activity of the mixture and low priority in the malaria program.

The 4-chloro-3-carbethoxyquinolines **5c, d,** and **e** reacted with 2-pyridyllithium giving the desired 4-chloro-3-quinolyl 2-pyridyl ketones **22c, d,** and **e** in 63, 27, and 63% yields, respectively. The 6,8-dichloro analog **5b**, however, gave the 2-pyridyl-α-di-(2-pyridyl)carbinol **23b** (43%; shown by ir (λ 1700 cm^{-1}) to contain a small amount of an unisolated pyridyl ketone). The corresponding acid chloride **10b** gave only the carbinol **23b** in 34% yield.

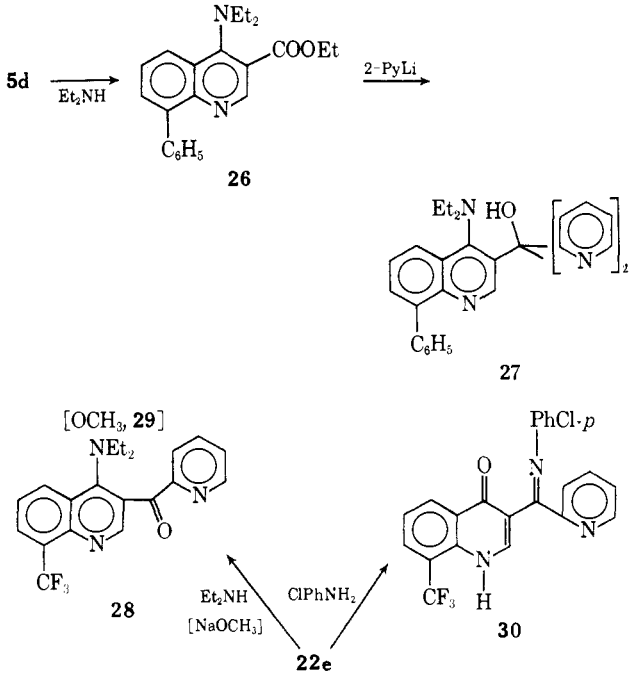
Approaches to the Synthesis of 4-Methoxy- and 4-Diethylamino-3-quinoline-α-aminomethanols.—4-Methoxy-3-quinolinecarboxylate esters **24b–e** were easily prepared by the action of NaOMe on the 4-chloro esters **5b–e**. A representative of these, **24b**, reacted with 2-pyridyllithium but gave a tripyridyl derivative, 2,4-di-(2-pyridyl)-3-quinolyl 2-pyridyl ketone (**25**, 44%) which evidently was contaminated with a small amount of unidentified material of molecular weight 440 (mass spectrum). The structure of **25** was established by elemental analysis and by ir, mass, and nmr spectra. It is of interest to compare the above reaction with that of $PhCH_2MgBr$ at the 4 position of 2-methoxyquinoline (which did not at the same time displace the 2-MeO group),[14] and to contrast it to the displacement of the EtO group of 2-ethoxyquinoline by BuLi.[15]



Displacement of the 4-Cl of the 8-Ph ester **5d** by NET_2 gave the 4-diethylamino ester **26** which then upon reaction with 2 equiv of 2-pyridyllithium gave the dipyridyl carbinol **27**.

8-Trifluoromethyl-4-chloro-3-quinolyl 2-pyridyl ketone (**22e**) reacted with Et_2NH and with NaOMe to give the corresponding 4-diethylamino and 4-methoxy derivatives **28** and **29**. However, the desired α-piperidylmethanols were not obtained from these by catalytic reduction. One attempt to prepare a 4-*p*-chloroanilino derivative from the pyridyl ketone **22e** by reaction with *p*-chloroaniline and acidic work-up, involved hydrolysis of the 4-Cl and gave the 4-quinolone ketoanil **30** the structure of which is supported by analysis and nmr and ir spectra.

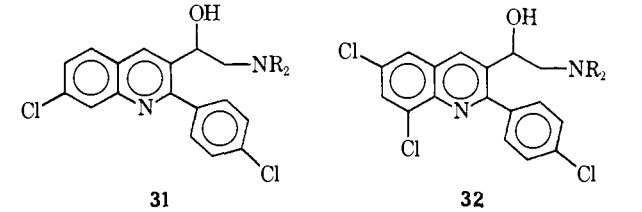
(14) R. C. Fuson, H. L. Johnson, and E. Grejshaber, *J. Org. Chem.*, **16**, 1529 (1951).
(15) H. Gilman and J. A. Beel, *J. Amer. Chem. Soc.*, **73**, 774, 32 (1951).



Because of unpromising pharmocological tests on the compounds **1**, **2**, and **3**, work on this series and on the several interesting unanswered chemical questions raised, has been suspended.

Biological Activity.—Antimalarial tests on compounds **1–3** were carried out on mice infected with *Plasmodium berghei* according to the method of Rane, *et al.*[16] Defining a drug as active when the mean survival time (MST) of the treated group is more than double that of controls (7.0 ± 0.5 days), and "curative" upon survival up to 60 days, **1 – 3** exhibited no antimalarial activity at the highest recorded dose level. The increases in survival times at 640 mg/kg in fractions of a day were: **1b**, 0.3; **1c**, 0.1 (at 320 mg/kg); **1d**, 0.4; **1e**, 9.4; **1g**, 0.5; **2b**, 0.5; **2e**, 0.3; and **3c**, 1.0.

In contrast to the above, six α-dialkylaminomethyl-2-*p*-chlorophenyl-3-quinolinemethanols (**31–32**) synthesized by Donovan and Smith [1d] possessed low antimalarial activities. The most active of these was **32b** which at 640 mg/kg increased the mean survival time 9.4 days.[16] This compound was phototoxic as determined by the method of Rothe and Jacobus; the minimum effective phototoxic dose was below 200 mg/kg in mice administered ip.[17] As a point of interest in this series, the 3-amino alcohol group must sterically interfere with the coplanarity and conjugation of the 2-aryl group with the quinoline nucleus, a conjugation with which the high phototoxicities in the 2-aryl-4-quinoline amino alcohols might possibly be associated.



(16) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Test data were supplied by the Walter Reed Army Institute of Research, Washington, D. C.

(17) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

Experimental Section[18]

3-Carbethoxy- and 3-carboxy-4(1*H*)-quinolones (4 and 9) were prepared according to published procedures for the parent,[3a] 8-Ph,[3b] 6-MeO,[3a] and 7-Cl[3c] compounds. Ph_2O was employed as cyclization solvent in all preparations of **4**.

Quinolinecarbonyl Chlorides (10, 12). A. 4,6,8-Trichloro-3-quinolinecarbonyl Chloride (10b).—DMF (2 ml) was added to a stirred refluxing slurry of 10 g (0.038 mole) of **9b** and 50 ml of $SOCl_2$; refluxing was continued for 4 hr. Excess $SOCl_2$ was distilled at atm pressure and the last traces removed by codistillation with dry C_6H_6. Crystallization of the residue from pet ether (60–110°) gave 9.85 g (86%) of the yellow acid chloride **10b**, mp 145–148°.

B.—**12b** and **e** were prepared as above but without DMF catalyst.

α-Bromomethyl-3-quinolyl ketones (13, 13') were prepared[7] through but without isolation of the intermediate diazomethyl ketones.

3-Quinolylethylene Oxides (14, 14'). A. 4,6,8-Trichloro-3-quinolylethylene Oxide (14b).—To a stirred slurry of 6.9 g (0.02 mole) of bromoethyl 4,6,8-trichloroquinolyl ketone (**13b**) in 50 ml of MeOH was added dropwise, over 10 min, a soln of 1.0 g (0.026 mole) of $NaBH_4$, 3 ml of 2 *N* NaOH, and 10 ml of H_2O. The solid dissolved almost immediately and after 20 min a ppt formed. After an additional 1 hr of stirring the pale yellow product was collected and oven-dried: 4.4 g (82%); mp 131–133°.

B.—A modification of the above procedure was necessary for **14'b** and **e**.

6,8-Dichloro-3-quinolylethylene Oxide (14'b).—A refluxing slurry of 8.74 g (0.0274 mole) of the bromomethyl ketone **13'b** in 50 ml of MeOH was removed from the heat source and stirred while a soln of 2.0 g (0.053 mole) of $NaBH_4$ in 10 ml of H_2O was added dropwise over 10 min. Addition of 5 ml of 2 *N* NaOH to the stirred, clear yellow soln caused pptn of **14'b**: 4.84 g (74%); pale yellow; mp 112–115°.

α-Di-*n*-butylaminomethyl-3-quinolinemethanols (1, 2). α-Di-*n*-butylaminomethyl-4,6,8-trichloro-3-quinolinemethanol (1b).—A stirred soln of 5.3 g (0.019 mole) of **14b** and 35 ml of *n*-Bu_2NH was heated at 135° for 18 hr. After excess reagent was removed by vac distillation the orange residue was dissolved in dry Et_2O, and **1** was fractionally pptd by Et_2O–HCl (the last fractions tended to gum; total crude yield; 6.28 g (74%); recrystd from EtOH–Et_2O, 4.20 g (49%); mp 178–180° dec.

3-Carbethoxy-4-chloroquinolines (5) were prepared by the reaction of the 3-carbethoxyquinolones **4a–g** with $POCl_3$ (3 moles, 3 hr, reflux); **5a** and **5f**[19] had previously been prepared employing a $POCl_3$–PCl_5 mixture.

3-Carbethoxy-8-trifluoromethyl-1,4-dihydroquinoline (7e).—A mixture of 4.0 g (0.013 mole) of **5e**, 0.84 g (0.015 mole) of KOH, 0.4 g of 10% Pd–C, and 25 ml of abs EtOH, was hydrogenated at 55° for 2.5 hr at 3.52 kg/cm². Filtration through Celite, concentration, and filtering gave **7e**: 2.19 g (61%); mp 158–159°; nmr ($CDCl_4$) δ 7.17 (m, 4), 6.50 (m, 1), 4.25 (m, 2), 3.79 (s, 2), 1.36 (t, 3).

3-Carbethoxy-6,8-dichloro-1,4-dihydroquinoline (7b).—To a stirred, ice-cooled soln of 6.0 g (0.16 mole) of $NaBH_4$ in 125 ml of 2-methoxyethanol was added portionwise 19.1 g (0.063 mole) of **5b**. The first addition caused temp rise to 60° and liberation of gas. The remainder of **5b** was then added over 1 hr. The slurry was stirred for 3 hr and the resulting ppt (**5b** and **7b**) was air-dried: 12.17 g (orange); mp 105–180°. Retreatment of this as above with 4 g of $NaBH_4$ in 125 ml of 2-methoxyethanol for 3 hr yielded 6.61 g (39%) of **7b** (orange): mp 187.5–189.5°; anal. sample (EtOH), mp 196° dec; nmr (DMSO-d_6) δ 8.64 (m, 1), 7.19 (m, 3), 4.11 (q, 2), 3.67 (s, 2), 1.22 (t, 3). The mother liquors poured into H_2O gave 6.88 g (oven-dried), mp 130–160°. Extraction with refluxing pet ether (bp 60–110°) removed unreacted **5b**: recrystd from EtOH, 2.1 g of **8b** (13%); mp 193–198°.

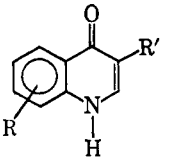
3-Carbethoxyquinolines (6). Catalytic Dehalogenation. 3-Carbethoxy-8-phenylquinoline (6d).—The following improved

(18) Instruments: (a) Melting points were obtained on a Thomas-Hoover apparatus, uncorrected; (b) anal. were correct ±0.4%; Gailbraith Lab. Inc., and Swartzkopf Microanalytical Lab; (c) sublimation of analytical samples was at 10–50° below the mp; (d) satisfactory spectra were obtained, for structural determination where required, and randomly in other cases, (e) ir, Perkin-Elmer 337; (f) nmr, Hitachi P-E R 20; (g) mass spectrograph, Hitachi P-E, RMU 6E.

(19) W. O. Kermack and N. Storey, *J. Chem. Soc.*, 1389 (1951).

TABLE II

3-FUNCTIONALIZED-4-QUINOLONES

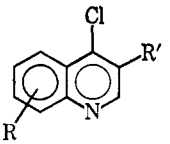


Compd	R	R′	Mp, °C[a]	% yield	Composition[e]
4b	6, 8-Cl_2	COOEt	305–308 dec[b]	74	$C_{12}H_9Cl_2NO_3$
9b	6, 8-Cl_2	COOH	300 dec[b]	100	$C_{10}H_5Cl_2NO_3$
4c	6, 8-Me_2	COOEt	273–276 dec[c]	68	$C_{14}H_{15}NO_3$
9c	6, 8-Me_2	COOH	298–300 dec[b]	100	$C_{12}H_{10}NO_3$
4e	8-CF_3	COOEt	209–213[c]	83	$C_{13}H_{10}F_3NO_3$
9e	8-CF_3	COOH	235 dec[d]	83	$C_{11}H_6F_3NO_3$
30	8-CF_3	C(2-Py)=NPhCl	199–200.5[c]	92	$C_{22}H_{13}ClF_3N_3O$[f]

[a] Dec, mp decomp. Recryst from: [b] DMF; [c] EtOH. [d] Analytically pure from reaction mixture. [e] Analyzed within ±0.4% for C, H; [f] for C, H, Cl, N.

TABLE III

3-FUNCTIONALIZED-4-CHLOROQUINOLINES

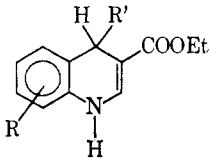


Compd	R	R′	Mp, °C	% yield	Composition[l]
10b	6, 8-Cl_2	COCl	145–147	90[a,b]	$C_{10}H_3Cl_4NO$
10c	6, 8-Me_2	COCl	103–105	38[a,b]	$C_{12}H_9Cl_2NO$
10d	8-Ph	COCl	125–126.5	90[a,b]	$C_{16}H_9Cl_2NO$[m]
10e	8-CF_3	COCl	94–95.5	70[a,b]	$C_{11}H_4Cl_2F_3NO$[m]
10g	7-Cl	COCl	137–139	38[a,b]	$C_{10}H_4Cl_3NO$
13b	6, 8-Cl_2	$COCH_2Br$	136–137.5	87[c]	$C_{11}H_5BrCl_3NO$
13c	6, 8-Me_2	$COCH_2Br$	76.5–78	58[a]	$C_{13}H_{11}BrClNO$
13d	8-Ph	$COCH_2Br$	132–133 dec	98[d]	$C_{17}H_{11}BrClNO$[m]
13e	8-CF_3	$COCH_2Br$	98–99	79[c]	(crude)
13g	7-Cl	$COCH_2Br$	104–106	83[a]	$C_{11}H_6BrCl_2NO$
14b	6, 8-Cl_2		132.5–134	82[e,b]	$C_{11}H_6Cl_3NO$
14c	6, 8-Me_2		95–96	91[a]	$C_{13}H_{12}ClNO$[i]
14d	8-Ph		140–141	83[f,b]	$C_{17}H_{12}ClNO$[i]
14e	8-CF_3		82–83	52[e]	$C_{12}H_7ClF_3NO$[k,m]
14g	7-Cl		153.5–155	83[c]	$C_{11}H_7Cl_2NO$
1b	6, 8-Cl_2	$CHOHCH_2NBu_2$	181–182 dec	74[g]	$C_{19}H_{25}Cl_3N_2O \cdot HCl$
1c	6, 8-Me_2	$CHOHCH_2NBu_2$	121–123 dec	66[g]	$C_{21}H_{31}ClN_2O \cdot HCl$
1d	8-Ph	$CHOHCH_2NBu_2$	174 dec	90[g]	$C_{25}H_{31}ClN_2O \cdot HCl$
1e	8-CF_3	$CHOHCH_2NBu_2$	172 dec	56[g]	$C_{20}H_{26}ClF_3N_2O \cdot HCl$
1g	7-Cl	$CHOHCH_2NBu_2$	168–170 dec	75[g]	$C_{19}H_{27}Cl_3N_2O \cdot HCl$
5b	6, 8-Cl_2	COOEt	109–110	87[f]	$C_{12}H_8Cl_3NO_2$[m]
5c	6, 8-Me_2	COOEt	76–77.5	97[f,b]	$C_{14}H_{14}ClNO_2$[m]
5d	8-Ph	COOEt	131–132.5	88[f]	$C_{18}H_{14}ClNO_2$[m]
5e	8-CF_3	COOEt	56–57	64[h]	$C_{13}H_9ClF_3NO_2$[m]
22c	6, 8-Me_2	COPy	148 dec	63[c]	$C_{17}H_{13}ClNO_2$
22d	8-Ph	COPy	102–103	27[c]	$C_{21}H_{13}ClN_2O$
22e	8-CF_3	COPy	155	63[c]	$C_{16}H_8ClF_3N_2O$
8b	6, 8-Cl_2	CH_2OH	196–198	13[c]	$C_{10}H_6Cl_3NO$[m]
8c	6, 8-Me_2	CH_2OH	166–169	53[c]	$C_{12}H_{12}ClNO$[m]

Recrystd from: [a] Pet ether (bp 60–110°); [b] sublimed; [c] EtOH; [d] crude, EtOH washed; [e] MeOH; [f] hexane; [g] EtOH–Et_2O; [h] pet ether (bp 30–60°). [i] C, calcd 66.81, found 65.99. [j] C: calcd 72.47, found 71.00. [k] C: calcd 52.67, found 52.13. [l] *Anal.*[18b] for C,H,N; [m] for C,H only.

TABLE IV

1,4-DIHYDRO-3-QUINOLINE CARBETHOXYLATES

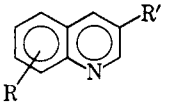


Compd	R	R'	Mp, °C	% yield	Composition[f]
7b	6, 8-Cl_2	H	196 dec[a]	39	$C_{12}H_{11}Cl_2NO_2$
7e	8-CF_3	H	158–159[b]	61	$C_{13}H_{12}F_3NO_2$
17a	H	2-Py	199–201[a,c]	0.7	$C_{17}H_{16}N_2O_2$[g]
17b	6, 8-Cl_2	2-Py	221–222 dec[d]	18	$C_{17}H_{14}Cl_2N_2O_2$
17e[e]	8-CF_3	2-Py	175–176[a]	20	$C_{18}H_{15}F_3N_2O_2$[h]

Recrystn solvent: [a] EtOH; [b] hexane; [c] sublimed; [d] 2-methoxyethanol. [e] Nmr ($CDCl_3$) δ 8.56 (d, 1), 7.32 (m, 8), 5.40 (s, 1), 4.10 (m, 2), 1.14 (t, 3). [f] *Anal.*[18b] C,H,N; [g] C: calcd 72.83; found 73.47; [h] for C,H only.

TABLE V

3-FUNCTIONALIZED QUINOLINES



Compd	R	R'	Mp, °C	% yield	Composition[m]
6b	6, 8-Cl_2	COOEt	131–133	96[a]	$C_{12}H_9Cl_2NO_2$
6c	6, 8-Me_2	COOEt	80.5–81	51[b]	$C_{14}H_{15}NO_3$[n]
6d	8-Ph	COOEt	106–107	54[c]	$C_{18}H_{15}NO_2$[n]
6e	8-CF_3	COOEt	88–89.5	73[c]	$C_{13}H_{10}F_3NO_2$[n]
6f	6-OMe	COOEt	85–87	66[b]	$C_{13}H_{13}NO_3$[n]
11b	6, 8-Cl_2	COOH	300–301 dec	94[d]	$C_{10}H_5Cl_2NO_2$[n]
11d	8-Ph	COOH	205–206	70[e]	$C_{16}H_{11}NO_2$[n]
11e	8-CF_3	COOH	208–209	78[c]	$C_{11}H_6F_3NO_2$[n]
12b	6, 8-Cl_2	COCl	170–172	92[a,f]	$C_{10}H_4Cl_3NO$
12e	8-CF_3	COCl	94–95	56[f,g]	$C_{11}H_5ClF_3NO$[n]
13'b	6, 8-Cl_2	$COCH_2Br$	197–199 dec	81[h]	$C_{11}H_6BrCl_2NO$
13'e	8-CF_3	$COCH_2Br$	142–143	66[c]	$C_{12}H_7BrF_3NO$
14'b	6, 8-Cl_2	CH—CH_2 (O)	118.5–120	74[g]	$C_{11}H_7Cl_2NO$
14'e	8-CF_3	CH—CH_2 (O)	65–67	72[f,g]	$C_{12}H_8F_3NO$
2b	6, 8-Cl_2	$CHOHCH_2NBu_2$	65–72 dec	38[i]	$C_{19}H_{26}Cl_2N_2O\cdot HCl$
2e	8-CF_3	$CHOHCH_2NBu_2$	90.5–92 dec	59[i]	$C_{20}H_{27}F_3N_2O\cdot HCl$
15c	6, 8-Me_2	COPy	97.5–98	27[a,f]	$C_{17}H_{14}N_2O$
15d	8-Ph	COPy	118–118.5	66[c,k,l]	$C_{21}H_{14}N_2O$[n]
15e	8-CF_3	COPy	99–99.5	58[c,l]	$C_{16}H_9F_3N_2O$[n]
15f	6-OMe	COPy	129–131.5	66[c]	$C_{16}H_{11}N_2O_2$
3	6, 8-Me_2	CHOHPip	143–148	15[f,h]	$C_{17}H_{22}N_2O$
16d	8-Ph	CHOHPy	137.5–138	64[c]	$C_{21}H_{16}N_2O$[n]

Recrystd from: [a] pet ether (60–100°), [b] (30–60°); [c] EtOH; [d] 2-methoxyethanol; [e] reaction product Et_2O washed; [f] sublimed; [g] hexane; [h] MeCN; [i] hygroscopic, not crystd; [j] EtOH–Et_2O; [k] prepared by the action of 2-PyLi on the 3-carboxylate ester; [l] by 2-PyLi on the 3-carboxylic acid (**15d**, 32%). [m] *Anal.*[18b] for C,H,N; [n] for C,H only.

method of Kaslow and Clark was used to prepare **6a**.[4] A suspension of 4.0 g (0.013 mole) of **5d** and 0.6 g of 10% Pd–C in 25 ml of glacial AcOH at 50° was hydrogenated (1 hr, 3.16 kg/cm²). Filtration through Celite, pouring into H_2O with stirring, collection of the ppt by filtration, and crystn from hexane gave 1.92 g (54%), mp 106–107°.

Sulfur Dehydrogenation of a 1,4-Dihydroquinoline. 3-Carbethoxy-6,8-dichloroquinoline (6b).—An intimate mixture of 11.9 g (0.044 mole) of **7b** and 3.13 g (0.097 mole) of S in a Wood's metal bath at 190°, was heated at 230° for 15 min (on fusion H_2S evolved vigorously). Cooling, extraction with 300 ml of refluxing pet ether (60–110°), filtering, concentrating to 125 ml, cooling, and recrystn of the yellow ppt from 250 ml of pet ether gave 11.43 g (96%), mp 132–134°.

4-Methoxy-3-carbethoxyquinolines (24). 4-Methoxy-6,8-dichloro-3-carbethoxyquinoline (24b).—A soln of 17.5 g (0.058 mole) of **5b** in 300 ml of MeOH was added to a soln of 0.17 mole of NaOMe in 150 ml of MeOH. After 1-hr reflux the mixture was poured into 2 l. of H_2O giving 13.9 g (80%), oven-dried, mp 141–142.5°.

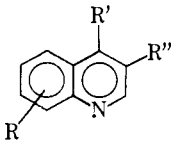
4-Diethylamino-8-phenyl-3-carbethoxyquinoline (26).—A soln of 6.2 g (0.02 mole) of **5d** and 4.4 g (0.06 mole) of Et_2NH in 100 ml of EtOH was refluxed for 2 hr. Cooling in ice returned 2.25 g (37%) of **5d**. Extraction of the residue from evapn of the filtrate with hexane, filtration to remove $Et_2NH\cdot HCl$, and evapn to dryness gave 3.1 g of **26**.

2-Pyridyllithium Reactions. A. With Carboxylic Acids 11 d,e. 2-Pyridyl 8-Phenyl-3-quinolyl Ketone (15d).—To a stirred soln of 2-pyridyllithium[8b,20] (from 11 g of 2-bromopyridine in 150 ml of anhyd Et_2O at −70° under N_2) was added rapidly

(20) J. P. Wilbaut, A. P. DeJonge, H. G. P. Van Der Voort, and P. Ph. H. L. Otto, *Recl. Trav. Chim. Pays-Bas*, **70**, 1043 (1951).

TABLE VI

3-FUNCTIONALIZED-4-SUBSTITUTED QUINOLINES

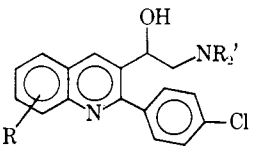


Compd[a]	R	R′	R″	Mp, °C	% yield[b]	Composition[k]
24b	6, 8-Cl_2	OMe	COOEt	141.5–143	80[c,d]	$C_{13}H_{11}Cl_2NO_3$[l]
24c	6, 8-Me_2	OMe	COOEt	83.5–85	56[d,e]	$C_{15}H_{17}NO_3$[l]
24d	8-Ph	OMe	COOEt	135.5–136	87[c]	$C_{19}H_{17}NO_3$[l]
24e	8-CF_3	OMe	COOEt	79.5–80	70[c]	$C_{14}H_{12}F_3NO_3$[l]
18b	6, 8-Cl_2	Py	COOEt	100–101.5	48[f]	$C_{17}H_{12}Cl_2N_2O_2$
18e	8-CF_3	Py	COOEt	64–66	15[f]	$C_{18}H_{13}F_3N_2O_2$
26	8-Ph	NEt_2	COOEt	72–74	72[e]	$C_{22}H_{24}N_2O_2$[l]
27[g]	8-Ph	NEt_2	C(OH)Py_2	200–201	14[f]	$C_{30}H_{28}N_4O$
28	8-CF_3	NEt_2	COPy	130.5–131	60[f]	$C_{20}H_{18}F_3N_3O$
29	8-CF_3	OMe	COPy	172.5–174	37[c,d]	$C_{17}H_{11}F_3N_2O_2$
23[h]	6, 8-Cl_2	Cl	C(OH)Py_2[h]	197–199	34[i,j]	$C_{25}H_{16}Cl_3N_4O$

[a] Py = 2-pyridyl. [b] Recryst from: [c] MeOH; [d] sublimed; [e] hexane; [f] EtOH. [g] Nmr ($CDCl_3$) δ 10.86 (s, 1), 8.87 (s, 1), 8.47 (d, 2), 7.51 (m, 14), 3.40 (m, 4), 1.05 (t, 6). [h] Also carries 2-(2-Py). [i] Prepared from acid chloride. [j] Prepared from ester, 47%. [k] *Anal.*[18b] for C,H,N; [l] for C,H only.

TABLE VII[a]

α-DIALKYLAMINOMETHYL-2-(*p*-CHLOROPHENYL)-3-QUINOLINEMETHANOLS[a]



Compd[a]	R	R′	Mp, °C	% yield	Composition[c]
31a	7-Cl	Et	113–115	72	$C_{21}H_{22}Cl_2N_2O$
31b	7-Cl	Bu	185–186.5	76	$C_{25}H_{30}Cl_2N_2O \cdot HCl$
31c	7-Cl	Heptyl	171–172.5	62	$C_{31}H_{42}Cl_2N_2O \cdot HCl$
32a	6, 8-Cl_2	Et	133–134	83	$C_{21}H_{21}Cl_3N_2O$
32b	6, 8-Cl_2	Bu	227.5–230	71	$C_{25}H_{29}Cl_3N_2O \cdot HCl$
32c	6, 8-Cl_2	Heptyl	162–164.5[b]	73	$C_{31}H_{41}Cl_3N_2O \cdot HCl$

[a] Synthetic route: 6-Cl-isatin, *p*-Cl-propiophenone → Q-3-CH_3, 4-COOH → Q-3-CH_3 → Q-3-COOH → Q-COCl → Q-$COCHN_2$ → Q-$COCH_2Br$ → Q-$CHOHCH_2Br$ → Q-CH—CH_2 (O) → **31** and **32**. [b] Solidifying and again melting at 177–178°. [c] *Anal.*[18b] C,H,Cl,N.

2.48 g (0.01 mole) of **11d**. After 10 min 50 ml of anhyd THF (distd from CaH_2) was added, and stirring at −70° was continued for 3 hr. The mixture was allowed to warm to 40° and 100 ml of H_2O was added rapidly. After filtration to remove the insol pyridyl ketone (other such ketones are sol in Et_2O) the Et_2O layer was washed twice with H_2O and evapd under reduced pressure, giving additional **15d**: recrystd from abs EtOH, 1.0 g (32%); mp 118–118.5°.

B. With Esters.—A THF soln of the ester was added to a two- to threefold excess of 2-pyridyllithium. Usually the product was isolated by evaporation of the Et_2O and crystallization of the residue from EtOH. In the prepn of **22d** and **27**, unreacted starting material crystallized first from EtOH. In a slightly different work-up, before further purification was carried out, unreacted starting ester was extracted from crude **15c** and **17b** with petroleum pentane (30–60°) and hexane, respectively.

8-Trifluoromethyl-4-(2 pyridyl)-1,4-dihydroquinoline (17e).—Reaction of ester **6e** (3.4 g, 0.013 mole), work-up as above, and fractional crystallization from EtOH yielded two products: **20**, 0.50 g (11%), mp 238.5–240°; ir (KBr disk), 3300 cm^{-1} (C-OH; no CO band); [*Anal.* ($C_{24}H_{18}F_3NO$) H, N; C: calcd 67.82; found 66.87; mol, wt calcd and found 393 (mass spectroscopy).] and **17e**, 0.88 g (20%), mp 175–176°; nmr ($CDCl_3$), δ 8.56 (d, 1), 7.32 (m, 8), 5.40 (s, 1), 4.10 (m, 2), 1.14 (t, 3). Compound **20** was dehydrogenated by S to yield a small amount of **21**, identified on the basis of the nmr spectrum which exhibited a sharp singlet at δ 7.59 (H-4) and an aromatic multiplet (δ 6.58–8.58).

2-Pyridyl 2,4-Di(2-pyridyl)-6,8-dichloro-3-quinolyl Ketone (25).—The 2-pyridyllithium reaction mixture was stirred for only 1 hr after addition of the ester **24b**. Crystallization from EtOH gave 44% of starting ester **24b**. Evaporation of the filtrate and column chromatography of the residue on Florisil (MeOH in C_6H_6–gradient elution) gave a red amorphorus solid which contained trapped solvent (by nmr). Crystallization from acetone (upon slow evaporation) gave 25% of **25** (yellow, true yield 45%); mp 234–238°; recrystd from MeCN, mp 239–241°, mol wt, calcd and found 457 (mass spectroscopy.). *Anal.* $C_{25}H_{14}Cl_2N_4O$: H,[18b] N,[18b] C, calcd, 65.66, found 66.28.

2-Pyridyl 4-Diethylamino-8-trifluoromethyl-3-quinolyl Ketone (28).—A soln of 1 g (2.96 mmoles) of **21e** and 0.896 g (11.8 mmoles) of Et_2NH in 15 ml of EtOH was refluxed for 1 hr. Ice-bath cooling gave 0.67 g (60%) of crude **28**.

2-Pyridyl 8-Trifluoromethyl-4(1*H*)-3-quinolonyl Ketone 4-Chlorophenylimine (30).—A mixture of 2 g (5.95 mmoles) of **22d** and 2.3 g (18 mmoles) of 4-chloroaniline in 75 ml of EtOH was refluxed for 1 hr. Concentrated HCl (1 ml) was added and refluxing continued for another hour. The mixture was cooled and quenched in ice–H_2O containing excess KOH. Crystallization of the ppt from EtOH gave 2.34 g (92%): nmr (DMSO)-d_6 δ 9.56 (s, 1), 8.79 (s, 1), 8.64 (d, 2), 8.25 (d, 1), 7.71 (m, 4), 6.81 (m, 4).

α-(2-Piperidyl)-6,8-dimethyl-3-quinolinemethanol (Stereoisomer Mixture 3c).—A slurry of 9.0 g of **22c** (0.03 mole), 250 ml of abs EtOH, 6 ml of concd HCl, and 0.75 g of PtO_2 was hydrogenated at 3.15 kg/cm^2. After absorption of $5H_2$, filtration through Celite, and concn to 30 ml, the soln was dild with H_2O and basified (NaOH). The Et_2O extract of the gummy ppt was washed with H_2O, dried ($MgSO_4$), and evapd. Treatment of the residual gum in 50 ml of Me_2CO with 75 ml of hexane and

cooling gave 3.12 g (28%), mp 115–131°. Recrystallization from pet ether (60°–110°) and sublimation [150°(0.1 mm)] gave 1.23 g (15%), mp 143–148° (sinters at 135°). An analytical sample was prepared by recrystn from MeCN: nmr ($CDCl_3$) δ 8.83 (d, 1, J = 2.5 Hz, H-2), 7.86 (q, 1, J = 2.5 Hz, nonequiv H-4 of diastereomers): 7.32 (s, 2), 4.85 (d, 0.41, J = 5 Hz), 4.56 (d, 0.59, J = 8 Hz), 4.21 (s, 2, NH,OH), 2.75 (s, 3), 2.46 (s, 3), 2.7 (m, 3), 1.45 (m, 6).

L(*S*)- and D(*R*)-3-Amino-1-phenylpyrrolidines. Stereoselective Antagonists for Histamine and Acetylcholine Receptors *in Vitro*

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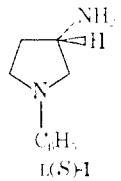
Studies leading to the synthesis of L(*S*)-3-amino-1-phenylpyrrolidine (**1**) and related L(*S*)- and D(*R*)-3-ethylamino analogs **11** are described. An ORD investigation is presented which defines the absolute configurations of intermediates and final products. Biological evaluation *in vitro* of racemic **11** shows both antihistaminic and anticholinergic activities. Pure L(*S*)-**11** exhibits a tenfold increase in antihistamine potency over D(*R*)-**11**. Essentially all of the anticholinergic activity is found in the D(*R*)-**11** enantiomorph. Other preliminary biological data obtained *in vivo* are also discussed.

Among biologically active compounds the arrangement of atoms >NCCR, where R = aryl, acyl-X, aryl-X, or some heterocycle and X = C, O, or N, is of major importance. This unit is found in such agonists as acetylcholine and norepinephrine; antagonists having a similar arrangement of atoms are exemplified by the cholinergic blocking agents and antihistamines. In other words, many autonomic drugs may be generally classified as β-aminoethyl analogs.

As part of a program designed to synthesize compounds of known absolute configuration for purposes of characterizing biological receptors on the basis of their stereoselective affinity towards various enantiomorphs, we explored a synthesis for optically pure L(*S*)-3-amino-1-phenylpyrrolidine analogs (**1**). This compound contains the units H_2N–C*–CN(Ph)– and H_2N–C*–C–CN(Ph)– with an asymmetric center (C*) located on the C α to the $-NH_2$ group. In this communication we report the synthesis of **1** from L(*S*)-aspartic acid (**2**), an optical rotatory dispersion investigation which defines the structures and absolute configurations of intermediates and final products, and some of our preliminary biological results *in vivo* and *in vitro* with two selected enantiomorphic analogs of **1**.



L(*S*)-**1**

Results and Discussion

Synthetic Aspects.—L(*S*)-Aspartic acid (**2**) serves as starting material. Initially, **2** was converted in 80% yield to the carbobenzoxy (Cbz) derivative (**3a**) through reaction with benzyl chloroformate in the presence of MgO in H_2O.[1] Derivatization of the amino group is required in order to render the amino N less nucleophilic and prevent its participation in subsequent reactions. The Cbz group was first investigated since it is easily removed under conditions employing mineral acid or by catalytic hydrogenation.[1,2] The Cbz derivative **3a** is converted into the corresponding anhydride **4a** by heating in Ac_2O. Reaction of anhydride **4a** with $PhNH_2$ in abs EtOH affords a mixture of α- and β-anilides (**5a** and **6a**), respectively.[3,4] The β-anilide **6a** is readily separated from the α isomer by selective crystallization from EtOH.[3,5] Heating the anilide mixture with Ac_2O affords Cbz-L(*S*)-α-amino-*N*-phenylsuccinimide (**7a**) in 70% yield. However, all attempts to remove the Cbz group under a variety of reaction conditions either afforded starting **7a** or products resulting from hydrolysis of the imide ring. Hydrogenation over Pd[2] in abs MeOH afforded the diketopiperazine dimer **8**; similar results were obtained by hydrogenation over Pd in HOAc–H_2O or EtOH–HOAc under analogous conditions.

Since the Cbz group proved difficult to remove without destruction of the imide system, we resorted to use of the *tert*-butyloxycarbonyl (Boc) group which is more easily hydrolyzed under acidic conditions.[6] Reaction of L(*S*)-aspartic acid (**2**) with *tert*-butyl azidoformate affords the Boc derivative **3b**. Heating **3b** in AcOH affords the anhydride **4b**. Reaction of **4b** with $PhNH_2$ in abs EtOH leads to the intermediate α- and β-anilides (**5b** and **6b**), respectively, in a combined yield of 40%. The anilide mixture is heated with Ac_2O affording the desired Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (**7b**). Reaction of **7b** in CF_3CO_2H, followed by treatment with Amberlite IRA-400 ion-exchange resin ($RN(CH_3)_3^+Cl^-$) yields a mixture of the HCl salts of imide **9** and anilide **10**. However, short reaction of Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (**7b**) with HCl gas in $CHCl_3$–C_6H_6 (3:1) affords L(*S*)-α-amino-*N*-phenyl-

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