The oil was found to be homogenous by v.p.c. and t.l.c., and its n.m.r. spectrum was identical with that of the corresponding 2-*p*-chlorobenzyl compound IXa, except for the phenyl region. A complex 4-proton pattern was obtained centering at about 7 p.p.m.

*Anal.* Calcd. for $C_{15}H_{20}FN$: C, 77.21; H, 8.64. Found: C, 77.29; H, 8.76.

**α-2′-Fluoro-2,5,9-trimethyl-6,7-benzomorphan (Xb).**—The tetrahydropyridine (IXb, 6.5 g.) was cyclized in 85% phosphoric acid (80 g.) at 185° for 45 hr. to give 6 g. of a dark brown oil. Both v.p.c. and t.l.c. indicated that the oil was a mixture of two components. Neither fractional distillation through a spinning-band column nor purification through a picrate derivative gave satisfactory separation of the compounds. The oil (2.0 g.) was successfully purified by preparative t.l.c., applying about 220 mg. of the mixture in 1 ml. of chloroform to each of 9 plates. The individual components were detected by spraying a corner of the plate, whereupon the individual silica gel containing components were scraped off the plates. They were extracted three times each with $CHCl_3$ and ether after adding dilute $NH_4OH$ to an aqueous suspension of the silica gel, since the compounds would not be removed from the silica gel without adding the base. A pale yellow oil was obtained from the extraction of the lower band. It was distilled to give 1.2 g. of a colorless oil (Xb). This was shown to be homogenous by t.l.c. and v.p.c. The n.m.r. spectrum was consistent with the structure of the desired product and very similar to the spectrum of Xa.

*Anal.* Calcd. for $C_{15}H_{20}FN$: C, 77.21; H, 8.64. Found: C, 77.05; H, 8.41.

A **hydrochloride** salt was prepared and recrystallized from a mixture of acetone and ether; m.p. 88–92°, followed by partial resolidification and complete melting at 208–212° dec.

*Anal.* Calcd. for $C_{15}H_{21}ClFN \cdot 1.5H_2O$: C, 60.69; H, 8.15; N, 4.71; active H, 1.37. Found: C, 60.19; H, 8.09; N, 4.59; active H, 1.41.

The **methiodide** of XIb melted at 260–261° dec.

*Anal.* Calcd. for $C_{16}H_{23}FIN$: C, 51.21; H, 6.18. Found: C, 51.45; H, 6.44.

**3,4-Dihydro-1,2-dimethyl-1-(2-dimethylaminoethyl)-7-fluoronaphthalene (XIIb).**—Methiodide XIb (1.7 g.) and 20 ml. of refluxing (1–2 hr.) 10% NaOH gave from ether extraction 1.2 g. of a colorless oil. Its n.m.r. spectrum, identical with that of XIIa except for the 3-proton aromatic region, showed singlets at 1.25 (5-$CH_3$) and 2.12 p.p.m. (N-$CH_3$), doublets at 0.87 ($J$ = 7 c.p.s., 9-$CH_3$) and 6.32 p.p.m. ($J$ = 9 c.p.s., α-styrene-type proton), and a quartet centered at 5.82 p.p.m. (β-styrene proton due to coupling with both the α-styrene and allylic hydrogen).

*Anal.* Calcd. for $C_{16}H_{22}FN$: C, 77.69; H, 8.96. Found: C, 77.95; H, 8.75.

**1,2-Dimethyl-7-fluoronaphthalene (XIIIb) Picrate.**—Compound XIIb (0.9 g.) as described for the aromatization of XIIa, gave, after distillation (125°, 0.1 mm.), 0.23 g. of colorless XIIIb (whose ultraviolet spectrum indicated a naphthalene structure) contaminated with a product that absorbed in the 0.8–1.2-p.p.m. region of the n.m.r. spectrum. A picrate was prepared and recrystallized from acetone–ethanol; m.p. 101–102°.

*Anal.* Calcd. for $C_{18}H_{14}FN_3O_7$: C, 53.60; H, 3.50; N, 10.42. Found: C, 53.84; H, 3.72; H, 10.43.

# Analgesics. Some Substituted 2,3-Dihydro-4-quinolones[1]

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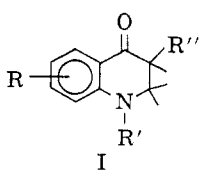
*Received March 9, 1965*

A number of substituted 2,3-dihydro-4-quinolones were prepared by the cyclization of the corresponding β-anilinopropionic acids. Several of these possessed analgesic activity. 1-(*p*-Toluenesulfonyl)-2,3-dihydro-4-quinolone and its 8-methoxy analog were converted to their enamines by reaction with pyrrolidine and alkylated with ethyl acrylate. The resulting products were hydrolyzed to yield 3-(2,3-dihydro-4-quinolone)propionic acid and its 8-methoxy analog. Derivatives of these compounds were examined for analgesic activity.

A series of substituted 2,3-dihydro-4-quinolones (I) were synthesized and examined for biological activity. These compounds were selected for study because of structural resemblances to morphine, meperidine, and other synthetic analgesics, and because the ring system provided a number of opportunities for molecular modification. In this study such modification included (1) replacement of the hydrogen atom on the heterocyclic nitrogen atom by alkyl, alkenyl, or aralkyl groups; (2) substitution on the aromatic ring; and (3) substitution on the carbon atom at the 3-position of I.




I

R = $CH_3$, Cl, $OCH_3$, or $OC_2H_5$
R′ = H, alkyl, allyl, or benzyl
R″ = $CH_2CH_2COR'''$

The desired 2,3-dihydro-4-quinolones (Table I) with substituents on the heterocyclic nitrogen atom or on the aromatic ring were prepared by the cyclization of the corresponding substituted β-anilinopropionic acids or by alkylation of substituted 2,3-dihydro-4-quinolones.

The required β-anilinopropionic acids were readily obtained by the addition of the substituted anilines to propiolactone[2] (Table II). This synthesis proved particularly advantageous when an N-alkylaniline was used and appeared simpler than the two-step synthesis which involved addition of the amine to an acrylic ester, followed by hydrolysis to give the β-anilinopropionic acid.[3] When the β-anilinopropionic acids were heated in polyphosphoric acid, satisfactory yields of the quinolones were obtained. Studies using thin layer chromatography indicated that at temperatures higher than those specified for the condensation, appreciable quantities of substituted anilines were formed. These undoubtedly resulted

(1) (a) This investigation was supported in whole by Public Health Service Research Grant AM 06432-02 from the National Institute of Arthritis and Metabolic Diseases. (b) Abstracted in part from the Ph.D. thesis of M. S. Atwal, University of Illinois at the Medical Center, 1964. (c) A portion of this paper was presented before the Division of Medicinal Chemistry, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1957).

(3) W. S. Johnson, E. L. Woroch, and B. G. Buell, *ibid.*, **71**, 1901 (1949).

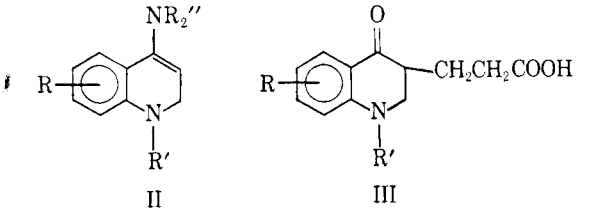
by the β-elimination of the amine from the β-anilinopropionic acid. Cyclization of a β-anilinobutyric acid to the corresponding 2,3-dihydro-4-quinolone had been reported,[4] but the generality of this reaction was not realized until this work was in progress.[5] Previous syntheses of 2,3-dihydro-4-quinolones involved cyclization of β-(arenesulfonamido)propionic acids by means of a variety of reagents, followed by vigorous hydrolysis of the 1-(arenesulfonyl)-2,3-dihydro-4-quinolone to give I.[3,6-10]

The cyclization by means of polyphosphoric acid was successful in almost all cases, but could not be employed for the synthesis of those compounds containing an allyl or benzyl group on the heterocyclic nitrogen atom. When N-benzyl- or N-allyl-β-anilinopropionic acid was heated in polyphosphoric acid, only 2,3-dihydro-4-quinolone could be isolated. The N-allyl and N-benzyl compounds were prepared by heating alcoholic solutions of 2,3-dihydro-4-quinolone with allyl or benzyl chloride. The alkylation of I was successful when small quantities of Triton B were added to the reaction mixture but did not yield alkylated products when sodium carbonate or sodium bicarbonate was substituted for the Triton B. Similar alkylations of the alkoxy-2,3-dihydro-4-quinolones with methyl iodide provided a more satisfactory synthesis of their N-methyl analogs than did the cyclization of the corresponding β-anilinopropionic acids.

While the cyclization of *ortho*- or *para*-substituted β-anilinopropionic acids could give rise to only one product, those with substituents in the *meta* position could yield either 5- or 7-substituted 2,3-dihydro-4-quinolones. Braunholtz and Mann[8] and Huisman and co-workers[10] had previously examined the structure of the product obtained by the cyclization of β-(N-*p*-toluenesulfonyl-*m*-anisidino)propionyl chloride. Although some disagreement exists concerning the presence of both possible isomers in the reaction mixture, it was agreed by both investigators that the chief product of the reaction was 1-(*p*-toluenesulfonyl)-7-methoxy-2,3-dihydro-4-quinolone. While it was expected that the polyphosphoric acid-catalyzed cyclization of β-(*m*-anisidino)propionic acid would yield chiefly 7-methoxy-2,3-dihydro-4-quinolone, the n.m.r. spectrum of this product was examined to obtain unequivocal proof of its structure. The spectra appeared to be in agreement with that reported by Huisman[10b] and Smith[11] and was used by us to establish the structure of the 7-ethoxy analog I (R′ = R″ = H).

We were interested in introducing a group in the 3-position of the 2,3-dihydro-4-quinolones. An attempt to carry out a Mannich reaction with 1-(*p*-toluenesulfonyl)-2,3-dihydro-4-quinolone, formaldehyde, and diethylamine yielded only starting materials. Mann,[12] who attempted the Mannich reaction directly on 1-methyl-2,3-dihydro-4-quinolone, observed that 1,3-dimethyl-2,3-dihydro-4-quinolone rather than the expected Mannich base was formed.

In view of the failures with the Mannich Reaction, it was decided to attempt to alkylate the ketone *via* the enamine. Attempts to prepare the enamine by the direct reaction of pyrrolidine and 1-methyl-2,3-dihydro-4-quinolone resulted in the isolation of starting products.[13] In order to increase the electrophilic nature of the carbon of the ketone group,[13] thus facilitating attack by an amine, 1-(*p*-toluenesulfonyl)-2,3-dihydro-4-quinoline[8] was treated with pyrrolidine and readily formed an enamine [II, R = H; R′ = *p*-$SO_2C_6H_4CH_3$;




II III

R″ = $(CH_2)_4$]. Compound II was alkylated by ethyl acrylate, but acrylonitrile and acrylamide did not react. The resulting ethyl 1-(*p*-toluenesulfonyl)-3-(2,3-dihydro-4-quinolone)propionate was hydrolyzed to give 3-(2,3-dihydro-4-quinolone)propionic acid (III, R = R′ = H; X = $CO_2H$).

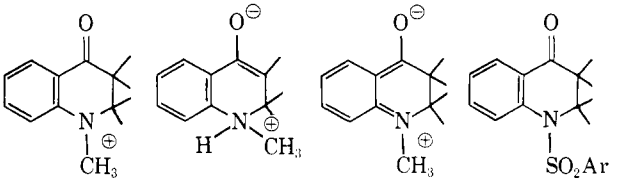
The enamine from 1-(*p*-toluenesulfonyl)-8-methoxy-2,3-dihydro-4-quinolone and pyrrolidine was similarly prepared, but the 7-methoxy analog failed to react with pyrrolidine. The enamine of 1-*p*-toluenesulfonyl-8-methoxy-2,3-dihydro-4-quinolone was successfully alkylated with ethyl acrylate and the product was hydrolyzed by acid to the corresponding acid III (R = 8-$OCH_3$; R′ = H; X = $CO_2H$).

3-(2,3-Dihydro-4-quinolone)propionic acid and its 8-methoxy analog were converted to the corresponding amides (Table III) *via* reaction of their mixed anhydrides with ammonia or amines.

3-(2,3-Dihydro-4-quinolone)propionpyrrolidide upon reduction with $LiAlH_4$ yielded 3-[3-(N-pyrrolidinopropyl)]-1,2,3,4-tetrahydro-4-quinolinol.

**Biological Activity.**—All of the compounds synthesized as well as the known 6-methyl-[6b] and 7-chloro-2,3-dihydro-4-quinolones,[3] which were made by the respective literature methods, were examined for analgesic activity using the Haffner tail pinch method[14]

(4) J. Koo, *J. Org. Chem.*, **26**, 2440 (1961).
(5) J. Koo, *ibid.*, **28**, 1134 (1963).
(6) (a) G. R. Clemo and W. H. Perkin, *J. Chem. Soc.*, **125**, 1608 (1924); (b) *ibid.*, **127**, 2297 (1925).
(7) (a) R. C. Elderfield, *et al.*, *J. Am. Chem. Soc.*, **68**, 1259 (1946); (b) *ibid.*, **71**, 1906 (1949).
(8) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 4166 (1957).
(9) C. D. Hurd and S. Hayo, *J. Am. Chem. Soc.*, **76**, 5065 (1954).
(10) (a) W. N. Speckamp, U. K. Pandit, and H. O. Huisman, *Rec. trav. chim.*, **82**, 39 (1963); (b) *Tetrahedron Letters*, **44**, 3279 (1964).
(11) H. Smith, G. H. Douglas, and C. R. Walk, *Experientia*, **20**, 418 (1964).
(12) P. I. Illyersh and F. G. Mann, *J. Chem. Soc.*, 467 (1958).
(13) It has been postulated that the yellow color of this ketone (A) might be explained by the ability of the compound to exhibit tautomerism and to exist as structure B.[6b,8] Structure C has also been suggested to be responsible for the yellow color.[8] This dipolar structure (C) would not favor enamine formation. Its contribution would be inhibited if an electron-attracting group were attached to the nitrogen atom (see structure D).

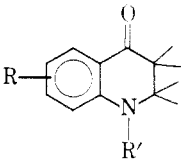



A B C D

(14) C. Bianchi and J. Froncheshini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

TABLE I

2,3-DIHYDRO-4-QUINOLONES

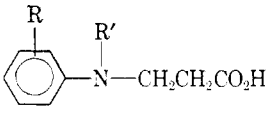


| R | R′ | Method | Temp., °C. | Time, hr. | B.p. (mm.) or m.p., °C. | Yield, % | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | A | 130 | 0.5 | 140–144 (0.2), 43.5[b] | 65 | | | | | | | |
| H | $CH_3$ | A | 135 | 3 | 120–122 (0.2) | 40 | $C_{10}H_{11}NO$ | ... | ... | 8.69 | ... | ... | 8.41 |
| H | $CH_3$ | B | ... | 48 | | 56 | | | | | | | |
| H | $C_2H_5$ | A | 145 | 12 | 125–130 (0.2) | 30 | $C_{11}H_{30}NO$ | ... | ... | 7.99 | ... | ... | 8.21 |
| H | $n$-$C_3H_7$ | A | 145 | 13 | 130–132 (0.2) | 25 | $C_{12}H_{15}NO$ | ... | ... | 7.40 | ... | ... | 7.51 |
| H | $n$-$C_4H_9$ | A | 150 | 13 | 130–133 (0.15) | 25 | $C_{13}H_{17}NO$ | ... | ... | 6.89 | ... | ... | 7.02 |
| H | $i$-$C_5H_{11}$ | A | 150 | 13 | 138–140 (0.15) | 20 | $C_{14}H_{19}NO$ | ... | ... | 6.45 | ... | ... | 6.52 |
| H | $C_6H_5CH_2$ | B | ... | 18 | 175–177 (0.2) | 70 | $C_{16}H_{15}NO$ | 80.98 | 6.37 | 5.90 | 81.09 | 6.28 | 5.97 |
| H | $CH_2$=$CHCH_2$ | B | ... | 24 | 125–127 (0.1) | 67 | $C_{12}H_{13}NO$ | 76.98 | 7.00 | 7.48 | 76.84 | 7.07 | 7.57 |
| 6-$OCH_3$ | H | A | 135 | 0.75 | 145–147 (0.2), 112–113[c] | 41 | $C_{10}H_{11}NO_2$ | ... | ... | 7.90 | ... | ... | 7.90 |
| 6-$OCH_3$ | $CH_3$ | B | ... | 42 | 160–165 (0.2) | 48 | $C_{11}H_{13}NO_2$ | 69.09 | 6.85 | 7.32 | 69.21 | 6.97 | 7.19 |
| 7-$OCH_3$ | H | A | 125 | 0.5 | 142–144 (0.2), 139[d] | | | | | | | | |
| 7-$OCH_3$ | $CH_3$ | B | ... | 36 | 155–157 (0.1), 73–74[f] | 60 | $C_{11}H_{13}NO_2$ | 69.09 | 6.85 | 7.32 | 69.29 | 6.74 | 7.41 |
| 7-$OCH_3$ | $C_6H_5CH_2$ | B | ... | 18 | 155–157 (0.2) | 66 | $C_{17}H_{17}NO_2$ | 76.38 | 6.41 | 5.24 | 76.24 | 6.10 | 5.24 |
| 8-$OCH_3$ | H | A | 150 | 0.75 | 140–145 (0.2) | 66 | $C_{10}H_{11}NO_2$ | ... | ... | 7.90 | ... | ... | 7.98 |
| 8-$OCH_3$ | $CH_3$ | B | ... | 22 | 155–160 (0.5) | 57 | $C_{11}H_{13}NO_2$ | ... | ... | 7.32 | ... | ... | 7.43 |
| 6-$OC_2H_5$ | H | A | 138 | 0.5 | 138–142 (0.1) | 55 | $C_{11}H_{13}NO_2$ | ... | ... | 7.32 | ... | ... | 7.68 |
| 7-$OC_2H_5$ | H | A | 135 | 0.5 | 144–145 (0.1) | 57 | $C_{11}H_{13}NO_2$ | ... | ... | 7.32 | ... | ... | 7.54 |
| 8-$OC_2H_5$ | H | A | 140 | 0.75 | 144–148 (0.2) | 67 | $C_{11}H_{13}NO_2$ | ... | ... | 7.32 | ... | ... | 7.66 |

[a] 2,4-DNP = 2,4-dinitrophenylhydrazone, 3,5-DNB = 3,5-dinitrobenzamide. [b] Lit.[3,6a] m.p. 43–44°. [c] Lit.[3,6b] m.p. 113–114°.

TABLE II

β-ANILINOPROPIONIC ACIDS



| R | R′ | B.p. (mm.) or m.p., °C. | Yield, % | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|
| H | H | 160–164 (0.2), 61[a] | 73 | $C_9H_{11}NO_2$ | ... | ... | 8.48 | ... | ... | 8.62 |
| H | $CH_3$ | 150–155 (0.2) | 75 | $C_{10}H_{13}NO_2$ | ... | .. | 7.82 | ... | ... | 7.86 |
| H | $C_2H_5$ | 155–157 (0.2) | 75 | $C_{11}H_{15}NO_2$ | ... | ... | 7.25 | ... | ... | 7.52 |
| H | $n$-$C_3H_7$ | 158–163 (0.2) | 70 | $C_{12}H_{17}NO_2$ | ... | . | 6.76 | ... | ... | 6.83 |
| H | $n$-$C_4H_9$ | | 72[b] | | | | | | | |
| H | $i$-$C_5H_{11}$ | | 65[b] | | | | | | | |
| H | $C_6H_5CH_2$ | 69 | 70 | $C_{16}H_{17}NO_2$ | 75.27 | 6.71 | 5.49 | 75.39 | 6.77 | 5.67 |
| $o$-$OCH_3$ | H | 87–88 | 60 | $C_{10}H_{13}NO_2$ | 61.53 | 6.71 | 7.17 | 61.63 | 6.65 | 7.30 |
| $m$-$OCH_3$ | H | 140–145 (0.2) | 70 | $C_{10}H_{13}NO_3$ | ... | ... | 7.17 | ... | ... | 7.25 |
| $p$-$OCH_3$ | H | 87–88[c] | 30 | | | | | | | |
| $o$-$OC_2H_5$ | H | 96 | 65 | $C_{11}H_{15}NO_3$ | 63.14 | 7.23 | 6.69 | 63.26 | 7.22 | 6.78 |
| $m$-$OC_2H_5$ | H | 145–150 (0.2) | 60 | $C_{11}H_{15}NO_3$ | 63.14 | 7.23 | 6.69 | 63.06 | 7.10 | 6.78 |
| $p$-$OC_2H_5$ | H | 104–105 | 58 | $C_{11}H_{15}NO_3$ | 63.14 | 7.23 | 6.69 | 63.30 | 7.24 | 6.83 |

[a] Lit.[2] m.p. 61–62°. [b] Tended to decompose on distillation *in vacuo* and was characterized as the hydrobromide. The crude ma-

| Derivative[a] | Crystn. solvent | M.p., °C. | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|
| HBr | Methanol–ether | 185 | $C_9H_{10}BrNO$ | 47.39 | 4.42 | 6.14 | 47.35 | 4.41 | 6.28 |
| 2,4-DNP | Acetic acid | 274–276 | $C_{15}H_{13}N_5O_4$ | 55.05 | 4.00 | 21.40 | 55.17 | 4.17 | 21.41 |
| 3,5-DNB | 95% Ethanol | 213–214 | $C_{16}H_{11}N_3O_6$ | 56.31 | 3.25 | 12.31 | 56.38 | 3.55 | 12.45 |
| HBr | Methanol–ether | 177–178 | $C_{10}H_{12}BrNO$ | 49.60 | 4.99 | 5.78 | 49.47 | 5.12 | 5.80 |
| 2,4-DNP | Acetic acid | 244–245 | $C_{16}H_{15}N_5O_4$ | 56.30 | 4.43 | 20.52 | 56.40 | 4.59 | 20.04 |
| HBr | Chloroform–ether | 184–186 | $C_{11}H_{14}BrNO$ | 51.58 | 5.51 | 5.47 | 51.70 | 5.67 | 5.36 |
| 2,4-DNP | Acetic acid | 246–248 | $C_{17}H_{17}N_5O_4$ | 57.46 | 4.82 | 19.71 | 57.61 | 4.99 | 20.02 |
| HBr | Chloroform–ether | 174–176 | $C_{12}H_{16}BrNO$ | 53.34 | 5.97 | 5.18 | 53.41 | 6.01 | 5.30 |
| 2,4-DNP | Acetic acid | 220–221 | $C_{18}H_{19}N_5O_4$ | 58.53 | 5.18 | 18.96 | 58.69 | 5.32 | 19.03 |
| HBr | Chloroform–ether | 138–139 | $C_{13}H_{18}BrNO$ | 54.92 | 6.38 | 4.92 | 55.02 | 6.46 | 5.01 |
| 2,4-DNP | Acetic acid | 166–167 | $C_{19}H_{21}N_5O_4$ | 59.52 | 5.52 | 18.27 | 59.67 | 5.63 | 18.41 |
| HBr | Chloroform–ether | 149–151 | $C_{14}H_{20}BrNO$ | 56.38 | 6.67 | 4.70 | 56.27 | 6.91 | 4.88 |
| 2,4-DNP | Acetic acid | 176–178 | $C_{20}H_{23}N_5O_4$ | 60.44 | 5.83 | 17.62 | 60.50 | 6.01 | 17.70 |
| HBr | Chloroform–ether | 157–158 | $C_{16}H_{16}BrNO$ | 60.37 | 5.07 | 4.40 | 60.32 | 5.10 | 4.45 |
| 2,4-DNP | Acetic acid | 210–211 | $C_{22}H_{19}N_5O_4$ | 63.30 | 4.59 | 16.78 | 63.48 | 4.60 | 16.72 |
| Picrate | 95% Ethanol | 210–211 | $C_{18}H_{16}N_4O_8$ | 51.93 | 3.87 | 13.46 | 51.51 | 3.85 | 13.33 |
| 2,4-DNP | Acetic acid | 190–192 | $C_{15}H_{17}N_5O_4$ | ... | ... | 19.06 | ... | ... | 18.58 |
| 2,4-DNP | Acetic acid | 290–293 | $C_{16}H_{15}N_5O_5$ | ... | ... | 19.60 | ... | ... | 19.90 |
| 2,4-DNP | Acetic acid | 254–255 | $C_{17}H_{17}N_5O_5$ | 54.98 | 4.61 | 18.86 | 54.92 | 4.53 | 18.91 |
| 2,4-DNP | Acetic acid | 264–266[e] | $C_{16}H_{15}N_5O_5$ | 53.78 | 4.23 | 19.60 | 53.99 | 4.11 | 19.50 |
| 2,4-DNP | Acetic acid | 241–242 | $C_{17}H_{17}N_5O_5$ | 54.98 | 4.61 | 18.86 | 55.09 | 4.76 | 18.85 |
| HBr | Methanol–ether | 200–202 | $C_{10}H_{12}BrNO_2$ | 46.52 | 4.68 | 5.43 | 46.59 | 4.58 | 5.39 |
| HBr | Methanol–ether | 181–182 | $C_{11}H_{14}BrNO_2$ | 48.54 | 5.18 | 5.14 | 48.72 | 5.28 | 5.14 |
| HBr | Chloroform–ether | 178–179 | $C_{11}H_{14}BrNO_2$ | 48.54 | 5.18 | 5.14 | 48.62 | 5.26 | 5.20 |
| 2,4-DNP | Acetic acid | 215–216 | $C_{17}H_{17}N_5O_5$ | 54.98 | 4.61 | 18.86 | 55.11 | 4.64 | 18.70 |
| HBr | Methanol–ether | 208–210 | $C_{11}H_{14}BrNO_2$ | 48.54 | 5.18 | 5.14 | 48.57 | 5.17 | 5.14 |
| 2,4-DNP | Acetic acid | 271–272 | $C_{17}H_{17}N_5O_5$ | 54.98 | 4.61 | 18.86 | 55.09 | 4.70 | 18.86 |

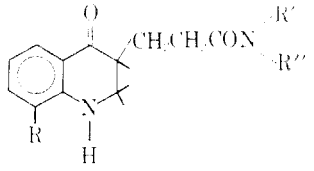
[d] Lit.[8,10a] m.p. 139°. [e] Lit.[8] m.p. 274°. [f] Recrystallized from benzene–methanol.

| Crystn. solvent | M.p., °C. | Formula | Hydrobromides: Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|
| Methanol–ether | 156–158 | $C_{10}H_{14}BrNO_2$ | 46.16 | 5.42 | 5.41 | 46.21 | 5.61 | 5.54 |
| Methanol–ether | 153–154 | $C_{11}H_{16}BrNO_2$ | 48.18 | 5.88 | 5.11 | 48.03 | 6.05 | 5.07 |
| Chloroform–ether | 158–160 | $C_{12}H_{18}BrNO_2$ | 50.00 | 6.29 | 4.86 | 50.00 | 6.25 | 4.68 |
| Chloroform–ether | 150–151 | $C_{13}H_{20}BrNO_2$ | 51.65 | 6.67 | 4.63 | 51.75 | 6.77 | 4.76 |
| Chloroform–ether | 136–138 | $C_{14}H_{22}BrNO_2$ | 53.16 | 7.01 | 4.43 | 53.00 | 6.93 | 4.52 |
| Chloroform | 124–125 | $C_{10}H_{14}BrNO_2$ | 43.50 | 5.11 | 5.07 | 44.04 | 5.07 | 5.16 |

terial was used in the next step of the synthesis. [c] Lit.[7a] m.p. 87–88°.

TABLE III

3-(2,3-DIHYDRO-4-QUINOLONE)PROPIONAMIDES



| R | R′ | R″ | Crystn. solvent | M.p., °C. | Yield, % | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | Ethanol | 197–198 | 82 | $C_{12}H_{14}N_2O_2$ | 66.04 | 6.47 | 12.84 | 66.17 | 6.39 | 12.77 |
| H | H | *n*-$C_4H_9$ | Ethanol–ether | 122–123 | 62 | $C_{16}H_{22}N_2O_2$ | 70.04 | 8.08 | 10.21 | 70.06 | 8.00 | 10.27 |
| H | | $-(CH_2)_4-$ | Chloroform–ether | 136–137 | 85 | $C_{16}H_{20}N_2O_2$ | 70.56 | 7.40 | 10.29 | 70.80 | 7.49 | 9.91 |
| $OCH_3$ | H | H | Ethanol | 167–168 | 80 | $C_{13}H_{16}N_2O_3$ | 62.89 | 6.50 | 11.28 | 63.04 | 6.49 | 11.28 |
| $OCH_3$ | H | *n*-$C_4H_9$ | Ethanol–ether | 105–106 | 65 | $C_{17}H_{24}N_2O_3$ | 67.08 | 7.95 | 9.20 | 67.26 | 8.10 | 9.15 |

and the hot plate method.[15] Of these compounds only 7-methoxy-, 1-methyl-, 1-methyl-8-methoxy-, and 1-methyl-7-methoxy-2,3-dihydro-4-quinolone when tested in mice possessed measurable analgesic activity. Substitution of the methyl group by other alkyl groups or substitution of the methoxy group by an ethoxy group resulted in the formation of compounds devoid of analgesic activity. In doses of 100 mg./kg. all of these compounds appeared to reduce the activity of mice and in larger doses produced sleep. The $LD_{50}$ values of all of these compounds are over 500 mg./kg. The $ED_{50}$ values for sleep and for analgesia, as determined using the Haffner tail pinch method on female Swiss white mice, are shown in Table IV.

TABLE IV

BIOLOGICAL ACTIVITY IN MICE OF SUBSTITUTED 2,3-DIHYDRO-4-QUINOLONES

| 2,3-Dihydro-4-quinolines | $ED_{50}$ (95% confidence interval), mg./kg.[a] Analgesia | Sleep |
|---|---|---|
| 7-Methoxy | 355 (237–533) | *b* |
| 1-Methyl | 250 (214–292) | 176 (153–213) |
| 1-Methyl-7-methoxy | 218 (165–288) | *b* |
| 1-Methyl-8-methoxy | 312 (235–415) | 359 (323–399) |

[a] $ED_{50}$ and the 95% confidence intervals were determined by the method of J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96,** 99 (1949). [b] No response produced by the maximum dose tested, 300 mg./kg.

## Experimental[16]

**General Procedure for the Synthesis of β-Anilinopropionic Acids.**—A solution of the appropriate aniline (1.0 mole) in acetonitrile (500 ml.) was heated to 81–83°. Propiolactone (1.0 mole) was added gradually with stirring over a period of 20–30 min. The heating and stirring was continued for 2–3 hr. after which time the solvent was removed *in vacuo* on a steam bath. The oily residue was dissolved in water (400 ml.) containing 40 g. of NaOH. The resulting solution was cooled in an ice bath and extracted several times with ether to remove unreacted aniline. The aqueous layer was acidified with HCl (1:1) to pH 4–5 to precipitate the β-anilinopropionic acid. This mixture was extracted several times with ether, and the organic phase was washed with water and dried ($MgSO_4$). The brown oil, resulting from the removal of the solvents, was fractionally distilled under vacuum. The acids were characterized as their hydrobromides. Their physical properties, yields, and analytical data are recorded in Table II. Several of the acids solidified and were crystallized from benzene–petroleum ether (b.p. 30–60°).

**2,3-Dihydro-4-quinolones. Method A. Cyclization of β-Anilinopropionic Acids.**—The appropriate β-anilinopropionic acid (0.1 mole) was added with constant stirring to polyphosphoric acid (450 g.) previously heated to 120°. The resulting solution was heated for the specified time at the designated temperature (Table I). Upon completion of the reaction, the resulting mixture was decomposed with ice (500 g.) and made alkaline with NaOH. This alkaline solution was extracted several times with a mixture of equal parts of ether and benzene. The combined extracts were then washed with water and dried ($MgSO_4$). After removal of the solvent the remaining viscous oil was distilled under vacuum, and the products so obtained were characterized. The yield, physical constants, and derivatives are listed in Table I.

**Method B. Alkylation of 2,3-Dihydro-4-quinolones.**—A solution of the 2,3-dihydro-4-quinolone (0.1 mole), Triton B (42 ml. of a 40% solution in methanol; 0.1 mole), and the desired halide (0.2 mole) was refluxed for the specified time. At the end of this period the solvent was removed by distillation and the residue was diluted with water. The pH was adjusted to 9, and the mixture was extracted with a mixture of equal volumes of benzene and ether. The combined extracts were dried ($MgSO_4$), the solvent was removed by distillation, and the residue was purified by distillation. The yields and physical constants are compiled in Table I.

**1-(*p*-Toluenesulfonyl)-4-(N-pyrrolidino)-1,2-dihydroquinoline.**—A solution of 1-(*p*-toluenesulfonyl)-2,3-dihydro-4-quinolone[5] (12.0 g., 0.04 mole), pyrrolidine (8.56 g., 0.12 mole), and *p*-toluenesulfonic acid (1.0 g.) in anhydrous benzene (100 ml.) was heated under reflux for 16 hr. using a Dean–Stark apparatus to trap the water formed in the reaction. The water was separated, and the solvent was removed by distillation. The residue was dissolved in absolute methanol (25 ml.), and the resulting solution was cooled until crystallization was complete. The crystals after filtration and drying weighed 11.0 g. and melted at 144–145°.

*Anal.* Calcd. for $C_{26}H_{28}N_2O_2S$: C, 67.81; H, 6.03; N, 7.95. Found: C, 67.45; H, 6.21; N, 7.90.

**1-(*p*-Toluenesulfonyl)-8-methoxy-2,3-dihydro-4-quinolone.**—A solution of 2,3-dihydro-4-quinolone (14.7 g., 0.1 mole) and *p*-toluenesulfonyl chloride (20.9 g., 0.11 mole) in pyridine (150 ml.) was refluxed for 3 hr. and then diluted with 200 ml. of water. The resulting solution was extracted with benzene to remove the expected compound. After distillation of the benzene 14.0 g. (43%) of a white solid was obtained. This compound after recrystallization from methanol melted at 150–151°.

*Anal.* Calcd. for $C_{17}H_{17}NO_4S$: C, 61.64; H, 5.20; N, 4.37. Found: C, 61.62; H, 5.17; N, 4.22.

**1-(*p*-Toluenesulfonyl)-4-(N-pyrrolidino)-8-methoxy-1,2-dihydroquinoline.**—A solution of 1-(*p*-toluenesulfonyl)-8-methoxy-2,3-dihydro-4-quinolone (13.2 g., 0.04 mole), pyrrolidine (8.6 g.,

(15) G. Woolfe and A. D. MacDonald *J. Pharmacol. Exptl. Therap.*, **80,** 300 (1944).

(16) All melting points are corrected and were determined by the capillary tube method using a Thomas–Hoover capillary melting point apparatus. Microanalyses were performed by Dr. Kurt Eder, Laboratoire Microchimique, École de Chimie, Genève, Switzerland, and by Micro-Tech Laboratories, Skokie, Ill. N.m.r. spectra were determined on a Varian Associates A-60 spectrometer, and infrared spectra on a Perkin-Elmer Model 337 spectrophotometer.

0.12 mole), and *p*-toluenesulfonic acid (1.0 g.) in anhydrous benzene (100 ml.) was refluxed for 18 hr. as described under the preparation of 1-(*p*-toluenesulfonyl)-4-(N-pyrrolidino)-1,2-dihydroquinoline. When the solvent was removed and the residue was recrystallized from methanol, a crystalline solid (10.0 g., 67%) melting at 141–142° was obtained.

*Anal.* Calcd. for $C_{21}H_{24}N_2O_3S$: C, 65.60; H, 6.29; N, 7.28. Found: C, 65.04; H, 6.16; N, 7.57.

**3-(2,3-Dihydro-4-quinolone)propionic Acid.**—1-(*p*-Toluenesulfonyl)-4-(N-pyrrolidino)-1,2-dihydroquinoline (10.6 g., 0.03 mole) was treated with ethyl acrylate (9.0 g., 0.09 mole) in boiling methanol (100 ml.) for 20 hr., after which time water (10 ml.) was added, and the mixture boiled for another hour. After removal of the methanol, the residue was extracted with ether, and the ether layer was washed with 5% HCl and dried ($Na_2SO_4$). The residue (9.0 g.) could not be crystallized nor distilled *in vacuo* and was immediately hydrolyzed by boiling with HCl (30 ml.) in acetic acid (30 ml.) and water (10 ml.) for 4 hr. Solvents were then removed *in vacuo*, and the residue was titrated with water (10 ml.). The solid was recrystallized from ethanol–ether to give crystals (4.3 g., 65% based on the enamine), m.p. 160–161°.

*Anal.* Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.74; H, 5.95; N, 6.39.

**3-(8-Methoxy-2,3-dihydro-4-quinolone)propionic Acid.**—When a solution of 1-(*p*-toluenesulfonyl)-4-(N-pyrrolidino)-8-methoxy-1,2-dihydroquinoline (3.8 g., 0.1 mole) and ethyl acrylate was boiled in methanol (100 ml.) for 20 hr. and worked up as described for the 8-desmethoxy analog, an oil (1.5 g.) was obtained. Hydrolysis of a 4.3-g. sample of such an oil was carried out with HCl (4.0 ml.) in acetic acid (12 ml.) and water (4.0 ml.) at reflux for 4 hr. Evaporation of the solvents and the addition of water (5 ml.) gave the product which crystallized from ethanol–petroleum ether (1.5 g., 60%), m.p. 139°.

*Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.62; H, 6.01; N, 5.61.

**Amides of 3-(2,3-Dihydro-4-quinolone)propionic Acid and the 8-Methoxy Analogs.**—To a suspension of acid (0.005 mole) in 100 ml. of anhydrous ether was added triethylamine (0.5 ml.). The resulting mixture was cooled to 5° and treated with ethyl chlorocarbonate (0.005 mole) and then stirred for 15 min. Ammonium hydroxide (5.0 ml.) or the amine (0.02 mole) was added, and the mixture was stirred an additional 15 min. The precipitated amide was removed by filtration, washed with water, and dried. The amides were purified by recrystallization from the designated solvent (see Table IV).

**3-[3-(N-Pyrrolidinopropyl)]-1,2,3,4-tetrahydro-4-quinolinol.**—To a solution of 3-(2,3-dihydro-4-quinolone)propion-N-pyrrolide (2.7 g., 0.01 mole) dissolved in tetrahydrofuran (40 ml.) was added in small quantities $LiAlH_4$ (1.5 g., 0.04 mole). The reaction mixture was warmed to 55–60° and stirred for 20 hr., at which time the excess $LiAlH_4$ was decomposed with 5% NaOH solution. Tetrahydrofuran was removed by distillation, and the reaction mixture was diluted with water and extracted three times with ether. The combined ether extracts were dried ($MgSO_4$), and the solvent was removed by distillation. The residue after recrystallization from ether weighed 1.25 g. (48%) and melted at 108°.

*Anal.* Calcd. for $C_{16}H_{24}N_2O$: C, 73.84; H, 9.29; N, 10.76. Found: C, 73.70; H, 9.44; N, 11.00.

# Chemistry and Pharmacology of Some Esters Derived from Basic Alcohols

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*Received March 25, 1965*

The preparation of a number of α-alkoxy-α,α-diphenylacetates derived from open-chain basic alcohols is described. Some of these compounds possess antitussive activity comparable to that of codeine phosphate and of the same order as that of their analogs which contain pyrrolidine or piperidine rings. 2-Diethylamino-1-(α-methoxy-α,α-diphenylacetoxy)propane rearranged on heating to 1-diethylamino-2-(α-methoxy-α,α-diphenylacetoxy)propane.

**Chemistry.**—2-Dimethyl- and 2-diethylaminoethyl α-alkoxy-α,α-diphenylacetates have been claimed to possess useful local anaesthetic, analgesic, or antispasmodic activity.[2] In a previous publication[3] we have described the preparation of some promising antitussives in which a number of α-alkoxy-α,α-diphenylacetic acids were esterified with a range of 1-alkylpyrrolidinyl or 1-alkylpiperidyl alcohols. In order to determine if a ring structure in the basic part of the molecule is essential for antitussive activity, we undertook the preparation of closely related compounds derived from open-chain basic alcohols carrying similar or different alkyl groups on the nitrogen atom. The basic esters were prepared from methyl or ethyl esters of the α-alkoxydiphenylacetic acids by transesterification with the appropriate amino alcohol.

During this synthetic work we observed the thermal rearrangement of 2-diethylamino-1-(α-methoxy-α,α-diphenylacetoxy)propane (I) to the isomeric 1-diethylamino-2-(α-methoxy-α,α-diphenylacetoxy)propane (II).

$$\underset{\text{Me}}{\underset{|}{\text{R—CH}_2\text{CHNEt}_2}} \xrightarrow{\Delta} \underset{\text{Me}}{\underset{|}{\text{RCHCH}_2\text{NEt}_2}}$$

I II

I and II, R = $Ph_2C(OMe)CO_2$

This rearrangement amplifies our earlier studies of the ester of the related 1-alkyl-2-hydroxymethylpyrrolidines[4a] and complements that of Kerwin, *et al.*,[4b] on 1-chloro-2-dialkylaminopropane.

## Experimental

Melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. The infrared absorption spectra for the ester rearrangement study were obtained by Mr. K. Austin using a Grubb-Parsons double-beam spectrometer with the specimens as approximately 2% solutions in $CHCl_3$.

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