

New Compounds

Some Diethylaminoethyl Ethers of Coumarins

SATYENDRA KUMAR¹

Department of Chemistry, Meerut College, Meerut, India

Received July 31, 1969

Some N-substituted aminoalkoxy derivatives of chromones² and flavones³ have been reported to possess marked antispasmodic activity. Coumarins are structurally similar to these γ -pyrones and possess interest-

ing biological properties.⁴ Therefore, some β -diethylaminoethyl ethers from coumarins have been prepared.

Experimental Section⁵

β -Diethylaminoethoxycoumarins.—To dry AcMe (50 ml) and anhydrous K_2CO_3 (0.15 mole), $Et_2N(CH_2)_2Cl \cdot HCl$ (0.15 mole) was added and the contents were thoroughly mixed. Hydroxycoumarin (0.01 mole) was then added with shaking. The reaction mixture was refluxed on a steam bath for 10 hr. Acetone was removed and after cooling H_2O was added to the residue. It was kept overnight and the solid was filtered, washed (H_2O), and crystallized from dilute EtOH. See Table I. Compounds **3** and **5** were characterized as picrates and **4** as the oxalate.

TABLE I
DIETHYLAMINOETHYL ETHERS OF SUBSTITUTED 7-HYDROXYCOUMARINS

No.	X	R ₁	R ₂	R ₃	R ₄	Formula ^a	Yield, %	Mp, °C
1	NEt ₂	H	Me	Cl	H	C ₁₆ H ₂₀ ClNO ₃	70	92
2	NEt ₂	H	Me	Br	H	C ₁₆ H ₂₀ BrNO ₃	68	86
3	NEt ₂ · C ₆ H ₅ N ₃ O ₇	CH ₂ C ₆ H ₅	Me	H	H	C ₂₃ H ₃₀ N ₃ O ₁₀	70	142
4	NEt ₂ · C ₂ H ₂ O ₄	H	Ph	H	H	C ₂₀ H ₂₅ NO ₇	75	170
5	NEt ₂ · C ₆ H ₅ N ₃ O ₇	H	Ph	Et	H	C ₂₉ H ₃₉ N ₃ O ₁₀	58	150
6	NEt ₂	Me	Me	Cl	H	C ₁₇ H ₂₂ ClNO ₃	72	120
7	NEt ₂	Et	Me	H	H	C ₁₈ H ₂₅ NO ₃	60	85
8	NEt ₂	<i>n</i> -Pr	Me	H	H	C ₁₉ H ₂₇ NO ₃	58	65
9	NEt ₂	H	Me	NO ₂	H	C ₁₆ H ₂₀ N ₂ O ₃	75	136
10	NEt ₂	H	Me	H	NO ₂	C ₁₆ H ₂₀ N ₂ O ₃	62	125

^a All compounds were analyzed for C, H, N.

- (1) Research Division, Cleveland Clinic, Cleveland, Ohio.
 (2) E. Kohlstaedt and K. M. Klinler, German Patent 1,018,874 (1957).
 (3) P. K. Jesthi, B. K. Sabat, and M. K. Rout, *J. Indian Chem. Soc.*, **42**, 105 (1965).

(4) P. K. Bose, *ibid.*, **35**, 367 (1958); T. O. Soine, *J. Pharm. Sci.*, **53**, 231 (1964).

(5) Melting points were taken in capillaries and are uncorrected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

The Reaction of Chloroquinolines with Formamides¹

NED D. HEINDEL AND PETER D. KENNEWELL

*Department of Chemistry, Lehigh University,
Bethlehem, Pennsylvania 18015*

Received August 18, 1969

Many medicinally important agents bear amino functions often incorporated by displacement of an "activated" halogen. We should like to report an extension of a previously described² technique to several

additional formamides and chloroquinolines and to call attention to the unusual behavior observed with monoalkylformamides.

Experimental Section

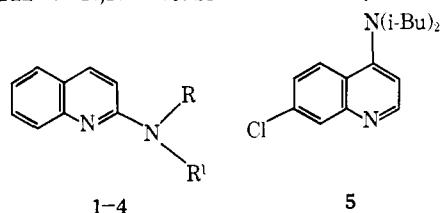
General Procedure for Aminoquinoline Synthesis.—A solution of 1 g of the chloroquinoline and 10 ml of the formamide (pre-dried by distillation over molecular sieves) was refluxed for 12 hr under a condenser protected by a $CaCl_2$ drying tube. The formamide solution was poured onto chopped ice and Na_2CO_3 solution (approximately 1 M) and extracted thoroughly (Et₂O). The ethereal layer was dried ($MgSO_4$) and evaporated, and the product was recrystallized or distilled *in vacuo* (see Table I).

General Procedure for Monoalkylformamides.—When 1 g of 2-chloroquinoline was refluxed for 12 hr with either N-methylformamide or N-*iso*-butylformamide and the reaction mixture then chilled, a 40 and 76% yield, respectively, of carbostyryl could be isolated by filtration. No aminoquinoline was detected in the

(1) Supported by Contract DA-49-193-MD-3011 from U. S. Army Medical Research and Development Command. This publication represents Contribution No. 687 from the Army Research Program on Malaria.

(2) N. D. Heindel and P. D. Kennewell, *Chem. Commun.*, 38 (1969).

TABLE I: N,N-DISUBSTITUTED AMINOQUINOLINES



Compld	Chloroquinoline +	Formamide	→	Product	Formula	Yield	Amine bp (mm) or mp, °C	Picrate mp, °C ^a
1	2-Chloro	HCON(<i>n</i> -Bu) ₂		R = R' = <i>n</i> -Bu	C ₁₇ H ₂₄ N ₂	88	130-133 (0.05)	178.5-180
2	2-Chloro	HCON(<i>i</i> -Bu) ₂		R = R' = <i>i</i> -Bu	C ₁₇ H ₂₄ N ₂	81	125-130 (0.1)	159-160
3	2-Chloro	HCONCH ₃ Ph		R = CH ₃ , R' = Ph	C ₁₆ H ₁₄ N ₂	36	161-163 (0.05)	172-174
4	2-Chloro	HCONHPh		R = H, R' = Ph	C ₁₅ H ₁₂ N ₂	35	97-98 ^b	
5	4,7-Dichloro	HCON(<i>i</i> -Bu) ₂		R = R' = <i>i</i> -Bu	C ₁₇ H ₂₃ ClN ₂	56	185-200 (0.2)	203-204

^a All liquid amines were analyzed as their crystalline monopicates (from EtOH) for the elements C, H, and N. Analyses were within $\pm 0.4\%$ of theoretical values. ^b P. Friedlaender and H. Weinberg, *Ber.*, **18**, 1532 (1885), reported mp 98°.

supernatant. Similarly, when 1 g of 4,7-dichloroquinoline was refluxed with either formamide or *N*-*iso*-butylformamide, 7-chloro-4(1H)-quinolone could be isolated in 86 and 65% yields, re-

spectively, mp 270-272°, lit.³ mp 277-279°.

(3) A. R. Surrey and H. F. Hammer, *J. Amer. Chem. Soc.*, **68**, 113 (1946)

Synthesis of 3-Bromo- and 3-Chloro-1-methyl-4-phenyl-4-propionoxypiperidines as Potential Analgetics

PHILIP M. CARABATEAS

*Sterling-Winthrop Research Institute,
Rensselaer, New York 12144*

Received August 7, 1969

Preparation of the title compounds was of interest to examine the effect of a halogen atom in the 3 position on the "reversed ester" of meperidine. Neither compound possessed analgetic activity.

Experimental Section¹

3-Bromo-1-methyl-4-phenyl-4-propionoxypiperidine Hydrobromide.—To a solution of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine² (17.3 g, 0.1 mole) in 100 ml of ice-H₂O and 5.2 ml of

concentrated H₂SO₄ was added *N*-bromoacetamide (13.8 g, 0.1 mole) all at once with stirring. After the addition of the NBA, 0.5 ml of H₂SO₄ was added. The temperature rose to 29° during the next 5 min. After 0.5 hr, another 0.5 ml of H₂SO₄ was added.³ Stirring was continued for 0.5 hr more at 35°, the solution was chilled in ice, basified with 35% NaOH solution, and extracted (Et₂O), and the extract was dried (Na₂SO₄) and treated with ethereal HBr. The Et₂O was decanted and the residual white gum was treated with 75 ml of Pr₂O. The gum dissolved in 0.5 hr and the resulting solution was allowed to stand for several days. The crystalline solid was collected and recrystallized from MeOH-EtOAc to give 19.0 g (46.7%) product, mp 168-169°. *Anal.* (C₁₅H₂₁Br₂NO₂) C, H, Br.

3-Chloro-1-methyl-5-phenyl-4-propionoxypiperidine Hydrochloride.—Similar treatment of the ethereal epoxide solution with ethereal HBr and (EtCO)₂O afforded 54.9% of product, mp 203-204° dec from EtOH. *Anal.* (C₁₅H₂₁Cl₂NO₂) C, H, Cl.

(1) Melting points were taken in open capillaries and are corrected. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

(2) C. J. Schmidle and R. C. Mansfield, *J. Amer. Chem. Soc.*, **78**, 428 (1956).

(3) After this work had been completed, the epoxide was reported by R. E. Lyle and W. E. Krueger, *J. Org. Chem.*, **30**, 394 (1965).

Book Reviews

Modern Separation Methods of Macromolecules and Particles.

Edited by THEO GERRITSEN, with 19 contributors. Wiley-Interscience, New York, N. Y. 1969. xi + 250 pp. 15.7 × 23.4 cm. \$14.95.

Advances in macrobiochemicals and synthetic polymers depend on the methodology of separating fractions, and ultimately compounds, of similar but not equal molecular weights and sizes. As we immerse ourselves more deeply in factors that may play a role in immunological disorders, the adequacy of separation methods of large molecules and of particulate aggregates will spell the success or failure of many a research project. The book under consideration is the work-up of a 1968 symposium. It comprises 11 chapters, ranging from pore "disc" electrophoresis, gel filtration, and chromatography to separations based on size and conformation. The subject is biologically oriented, two chapters being devoted to lymphocyte separation. Anyone working on proteins, fats, polysaccharides, polynucleotides, enzymes, cells differentiated by size and morphology, and similar particles from large molecules to colloid suspensions will learn something new and useful from these surveys.

UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VIRGINIA

ALFRED BURGER

Induction of Ovulation. By RODNEY P. SHEARMAN. Charles C Thomas, Publisher, Springfield, Ill. 1969. xi + 142 pp. 23.5 × 16 cm. \$11.50.

This slender volume will serve as a useful survey of methods to induce ovulation in anovulatory women, whose usual problem is gonadotropin disorder. Apart from the chapter on surgical intervention, the medicinal chemist will find interest in the application of clomiphene and of cyclofenil (Sexovid®) (!) and human gonadotropins to anovulation, as well as in the spontaneous cures and placebo effects which ameliorate this condition. The pharmacology of compounds used to induce ovulation is explained nicely. For the more primitively motivated reader, there are ample photographic illustrations of virilization and hirsutism, and for the historically minded there is a retrospective section going back to ancient Egypt, when amenorrhea and irregular menstruation were treated with "douches of garlic and wine and the ingestion of wam grease and sweet beer." The rest of the booklet offers carefully documented chapters with 343 references and an adequate index.

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