Sodium di-*n*-butylmalonate was obtained by adding, under anhydrous conditions, the theoretical amount of di-*n*-butyl malonate into the standardized sodium *n*-butoxide solution. This solution was prepared immediately before use.

The proper quantity of dichlorobenzoate was weighed into a volumetric flask and an aliquot of sodium di-*n*-butylmalonate was added. The mixture was made up to volume with dry *n*-butyl alcohol. The solid dichlorobenzoate was dissolved by careful warming and shaking. Aliquots of this solution were pipetted into soft glass ampoules which were then sealed and heated for the required length of time at 104.7 ± 0.1°.

After heating, the tubes were cooled and crushed under 50.00 cc. of absolute methanol. The resulting solution was titrated with standard perchloric acid using *m*-cresol purple to determine the end-point. The original concentration of dichlorobenzoate (a) was determined from its weight and the volume of the solution, and the original concentration of the sodium di-*n*-butylmalonate (b) by removing two of the soft glass ampoules from the thermostat after 5 minutes and titrating as described above (zero time was taken as being 5 minutes after the tubes were immersed in the thermostat). The determination of the order in dichlorobenzoate and malonic ester anion was carried out by the same procedure.

Rate of Solvolysis of the Dichlorobenzoates.—Weighed portions of the 2,6-dichlorobenzoates were made up to volume with dry *n*-butyl alcohol. The solid esters were dissolved by shaking and heating. Aliquots of the resulting solutions were sealed in soft glass ampoules and heated at 104.7 ± 0.1° for timed intervals. The ampoules were cooled and crushed under 50.00 cc. of absolute methanol, and the resulting solutions were titrated with standard aqueous sodium hydroxide solution using brom thymol blue to find the end-point. The rate constant, k_1, was calculated from the original concentration (a) of the ester derived from the weight of ester used and the volume of the solution.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY]

The SN2′ Reaction. III. Structure and SN2′ Reactions of the Halocodides

BY GILBERT STORK AND FRANK H. CLARKE

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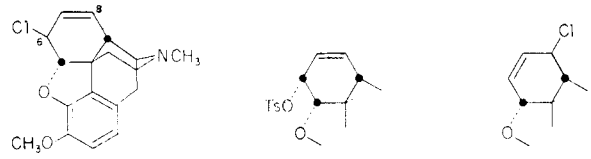
Structures previously assigned[1] to the halocodides are confirmed. The general occurrence of SN2′ displacements with these substances is corroborated by studying the kinetics of the displacement reaction of piperidine on α-chlorocodide.

Some time ago structures were advanced for the halides derived from codeine and its isomers, the so-called halocodides, and the conclusion was reached that SN2′ mechanisms are generally involved in the reactions of these substances.[1] We now wish to present the evidence which verifies our earlier postulates.

α-Chlorocodide has been shown to have its chlorine at C_6[2] and must have the stereochemistry shown in I[3] for reasons which we have discussed previously.[1] We have further confirmed this



I II III

stereochemical assignment by showing that α-chlorocodide is formed in quantitative yield from the reaction of codeine tosylate, II[4] with lithium chloride in acetone. Since α-chlorocodide is unstable and rearranges on heating to β-chlorocodide,[5] the formation of the α-isomer must be the direct product of normal bimolecular displacement with inversion (see reaction of codeine tosylate with piperidine below).

β-Chlorocodide has been postulated to be the C_8 allylic isomer of α-chlorocodide.[6] That this assignment is valid follows from the reactions of the substance[1] which require that it be either the C_6 epimer of the α-compound or a C_8 allylic isomer. Only the latter formulation is compatible with the lack of reaction with potassium iodide in methanol of β-chlorocodide, as we have now shown that codeine tosylate reacts readily with iodide ion. β-Chlorocodide is then the C_8 isomer with the hindered back side and has the structure and stereochemistry shown in III.

We have now established that bromocodide and

(1) G. Stork in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, New York, N. Y., 1952, pp. 176–189.

(2) L. F. Small, B. F. Faris and J. E. Mallonee, *J. Org. Chem.*, **5**, 334 (1940).

(3) This is based on the stereochemistry that we have considered established for morphine and codeine, ref. 1, p. 171. Our conclusions have been confirmed recently by the X-ray work of M. Mackay and D. Crowfoot Hodgkin, *J. Chem. Soc.*, 3261 (1955).

We take this opportunity to answer some remarkable assertions by Bentley, *et al.*: (a) Bentley and Thomas, *J. Chem. Soc.*, 3237 (1955), apparently do not realize that *further evidence has to be provided* when a structure is proposed which is based on mechanisms without analogy. (b) Bentley and Cardwell, *ibid.*, 3245 (1955), attribute to us the implication that ethanol is *mechanistically* required in the reduction of thebaine with sodium in liquid ammonia. We merely stated that we obtained good results *only* in the presence of alcohol. This is a statement of fact. Bentley and Cardwell go to some length to show that the alcohol may be omitted by using thebaine which has gone through an 80-mesh sieve. We prefer the simpler expedient of using ethanol. (c) Bentley and Cardwell, *ibid.*, 3252 (1955), misquote us: "This disposes of Stork's attempt . . . ("The Alkaloids" . . . Vol. II, 171)" is followed by "Stork's subsequent attempt (ref. 1, p. 190)." The fact is that the whole discussion of the relationship of the ethanamine chain and the oxide bridge is on pp. 173–174. Far from disposing of our "attempt to deduce the stereochemistry of morphine . . ." the discussion of Bentley and Cardwell does not seem compatible with the evidence. We take very strong objection to the statement that "to maintain this argument [Stork] subsequently (ref. 1, p. 191) overlooks the fact that the Hofmann degradation . . . involves a *cis* elimination . . ." Not only did we *not* overlook it, but we *took pains to emphasize it* by writing the reaction *not* as a concerted *trans* but as a non-concerted *cis*-elimination!

(4) P. Karrer and G. Widmark, *Helv. Chim. Acta*, **34**, 34 (1951); H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951).

(5) L. F. Small and F. S. Palmer, *ibid.*, **61**, 2186 (1939).

(6) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II Academic Press, New York, N. Y., 1952, p. 63.

iodocodide are correctly represented by IV and V and correspond to β-chlorocodide

IV V

The infrared spectra (Fig. 1) of β-chlorocodide, bromocodide and iodocodide are almost identical and are all characterized by a very strong band at 11.1 μ which is absent from the spectrum of α-chlorocodide, while the latter possesses a strong band at 10.7 μ which is missing from the spectra of the other three. Also, the molecular rotation differences between the halo compounds and the corresponding parent hydrogen compounds (Δ⁷- and Δ⁶-desoxy-codeine, VII and VI, respectively) are $\Delta_{\alpha Cl} = -1019$; $\Delta_{\beta Cl} = +528$, $\Delta_{Br} = +766$ and $\Delta_{I} = +1121$.[7] Obviously, both bromocodide and iodocodide are related structurally to β-chlorocodide and not to α-chlorocodide.

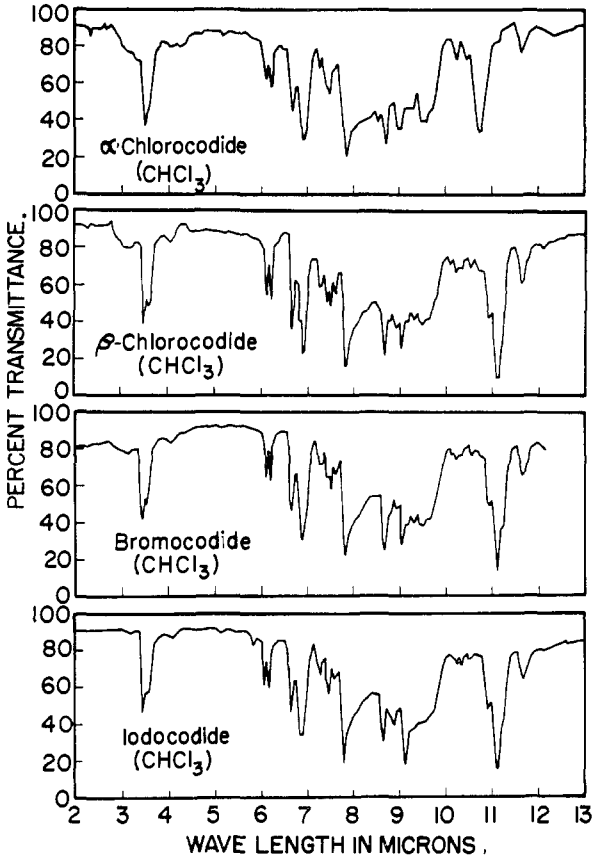
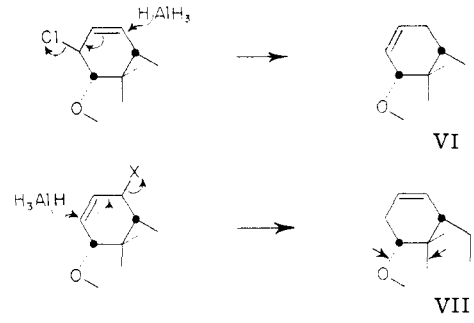


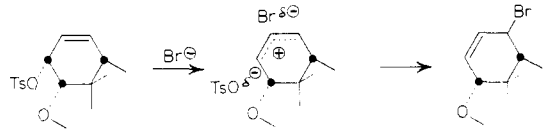
Fig. 1.

An interesting chemical confirmation of these structural assignments has been found in the behavior of the four halocodides toward lithium aluminum hydride: α-chlorocodide produced only Δ⁶-desoxycodeine (VI), while from β-chlorocodide, bromocodide and iodocodide only Δ⁷-desoxycodeine (VII), could be isolated



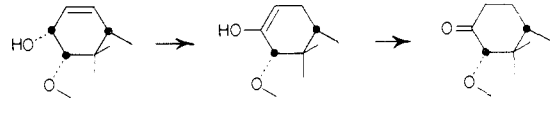
VI VII

It has been noted above that α-chlorocodide isomerizes readily to β-chlorocodide. This markedly greater stability of the halocodides with a Δ⁶-double bond is remarkable. In the case of the bromo and iodo compound the ease of rearrangement to the stable series is such that the Δ⁷-isomer corresponding to I cannot be obtained. We have found that even displacement of codeine tosylate (II) with lithium bromide or sodium iodide in acetone leads only to bromocodide (IV) and iodocodide (V). Either the expected 6-halo compound is formed and rearranges very rapidly or it is never actually present, the reaction conceivably being represented as



The position of the equilibrium is undoubtedly determined by the higher energy of the Δ⁷-isomers. This becomes understandable when one considers that in the Δ⁷-compounds, such as VII, the angle between the two bonds marked by arrows in VII is greater than it is in VI, resulting in greater strain attending the *cis* fusion of the oxide ring in the former.[8]

SN2′ Reactions of the Halocodides.—Displacement reactions of the halocodides take place by SN2′ mechanisms.[1] The reactions with lithium aluminum hydride which have been mentioned above are especially interesting examples which can be explained only as has just been illustrated since the same olefin, presumably VI, would have resulted from either I or II *via* a carbonium ion mechanism.[9] For the same reason the reactions of I and III with ethyl mercaptide anion or with piperidine[1] *must be concerted reactions with rearrangement, at least in the case of one of the two isomeric halides.* We have indeed stated that these



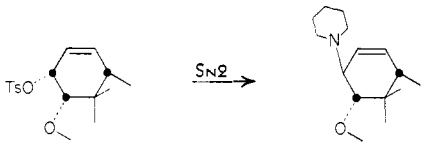
(7) These molecular rotation differences are large enough so that the fact that the rotations of α-chlorocodide and of iodocodide were measured in chloroform while the other substances were measured in ethanol does not affect the sign of the differences.

(8) *Cf.* E. J. Corey and R. A. Sneen, THIS JOURNAL, **77**, 2505 (1955). A particularly interesting illustration of the greater stability of VI than VII is encountered in the catalytic isomerization of codeine to dihydrocodeinone over palladium (*cf.* ref. 6, p. 39).

(9) For another illustration of rearrangement with lithium aluminum hydride see L. F. Hatch and J. J. D'Amico, *ibid.*, **73**, 4393 (1951).

reactions represent the first clear-cut illustrations of the occurrence of the SN2′ mechanism.[1,10,11] This view has been criticized by England[12] on the ground that bimolecular kinetics have not been demonstrated for these reactions. Since, however, the reaction of the two halocodides, *e.g.*, with piperidine, gives two *different* piperidocodides, with rearrangement in either case, it is clear that *both* reactions cannot be proceeding *via* carbonium ions, and kinetic evidence, although desirable, is not required to demonstrate SN2′ reactions with these halides.

We have now subjected the displacement reaction of the chlorocodides with piperidine to further scrutiny. It is known that the piperidocodide VIII formed by heating β-chlorocodide III with piperidine has the piperidine residue at C_6.[5] We have demonstrated the orientation of the piperidine residue in 6-piperidocodide (VIII) by showing that the substance is formed in high yield by heating codeine tosylate (II) with piperidine in benzene or toluene solution. The kinetics of this reaction were found to be second order, and the reaction is therefore a simple bimolecular displacement with inversion as illustrated below



VIII

The reaction of α-chlorocodide (I) with piperidine[13] gives a piperidocodide, IX in which the piperidine is attached at C_8.[5] This reaction with α-chlorocodide is very much more rapid than the corresponding reaction of β-chlorocodide (see Experimental part) and should either reaction involve an SN1 mechanism it would very likely be the former. As a matter of fact, we will see that that reaction is bimolecular and therefore an example of SN2′ displacement.

Kinetic Results.—The kinetics were studied by heating at 59.07 ± 0.01° and at 70.00 ± 0.01°, for varying lengths of time, mixtures of α-chlorocodide and piperidine in benzene solution. The extent of reaction was determined by titration of the free chloride ion, substantially by the method of Young, Webb and Goering.[14]

The rate constants were calculated on the basis of the following reactions, the first of which is rate-determining

α-chlorocodide + piperidine ⟶ 8-piperidocodide·HCl

8-piperidocodide·HCl + piperidine ⟶ 8-piperidocodide + piperidine·HCl

Because of the insolubility of piperidine hydrochloride in benzene, the piperidine consumed is twice the chloride ion produced.

(10) G. Stork and W. N. White, THIS JOURNAL, **75**, 4119 (1953).
(11) G. Stork and W. N. White, *ibid.*, **78**, 4604 (1956).
(12) B. D. England, *J. Chem. Soc.*, 1615 (1955).
(13) E. Von gerichten and F. Müller, *Ber.*, **36**, 1590 (1903).
(14) W. G. Young, I. D. Webb and H. L. Goering, THIS JOURNAL, **73**, 1076 (1951).

We have then $k_1 = 2.303/t.\ \log(a/(a - x))$, and since $dx/dt = k_2(a - x)(b - 2x)$

$$k_2 = \frac{2.303}{t(b - 2a)} \log \frac{a(b - 2x)}{b(a - x)}$$

where a is the initial concentration of α-chlorocodide, in moles per liter, b is the initial concentration of piperidine in moles per liter, x is the concentration of chloride ion formed in time t (seconds), k_1 is the first-order rate constant in reciprocal seconds and k_2 is the second-order rate constant in liters mole^{-1} sec^{-1}. In run I the value of $b - 2a$ (0.0009 mole/liter) has only one significant figure, and an approximate form of the integrated rate equation was used. If we let $b = 2a + 2\Delta$ we get $dx/dt = 2k_2(a - x)(a + \Delta - x)$ and

$$2k_2t = \left(\frac{1}{a - x} - \frac{1}{a}\right) - \frac{\Delta}{2}\left(\frac{1}{(a - x)^2} - \frac{1}{a^2}\right)$$

Only the first term in Δ is needed to obtain accurate values of k_2 since Δ is very small.

The third-order rate constant k_3 was calculated in run I, assuming a reaction first order in chlorocodide and second order in piperidine

$$dx/dt = k_3(a - x)(b - 2x)^2$$

In this case, b is squared, and since $b - 2a$ is less than 1% of $2a$, we may replace b by $2a$; we then have

$$dx/dt = 4k_3(a - x)^3 \text{ and } k_3 = \frac{1}{8t} - \frac{1}{(a - x)^2} - \frac{1}{a^2}$$

All concentrations were corrected for the volume expansion of benzene by multiplying the concentration calculated at 25° by the ratio of the density of benzene at 25° and at the temperature of the run.[15]

The results are shown in Tables I and II and are illustrated in Figs. 2 and 3.

It is obvious from Table I that the first-order rate "constant" k_1 decreases steadily as the reac-

TABLE I

RATE OF REACTION OF α-CHLOROCODIDE WITH PIPERIDINE IN BENZENE SOLUTION AT 59.07 ± 0.01°

Run I, a = 0.0789; b = 0.1587

Time, hr.	0.01030 N $AgNO_3$, ml.	10^4k_1, sec.$^{-1}$	10^3k_2, l./mole sec.	10^3k_3, l./mole^2 sec.	% Reaction
2.75	5.9	1.33	8.91	6.08	12.2
5.75	10.4	1.19	8.48	6.16	21.8
10.75	16.7	1.11	8.69	7.33	34.8
17.75	22.2	0.97	8.47	7.74	46.3
24.10	25.7	.89	8.36	8.44	53.7
31.90	29.3	.82	8.57	9.80	61.1

Mean k_2 = 8.58 ± 0.15

TABLE II

SUMMARY OF KINETIC RESULTS FOR THE REACTION OF α-CHLOROCODIDE WITH PIPERIDINE IN BENZENE SOLUTION

Run	Temp., °C. ± 0.01°	a	b	10^3k_2, l./mole. sec.	% Reaction
I	59.07	0.0789	0.1587	8.58 ± 0.15	12.2–61.1
II	59.07	.0803	.3166	8.42 ± .19	16.6–81.6
III	70.00	.0781	.2355	16.7 ± .2	17.7–72.5
IV	70.00	.0718	.5082	16.7 ± .4	35.6–82.5

All concentrations were corrected for the volume expansion of benzene by multiplying the concentration calculated at 25° by the ratio of the density of benzene at 25° and at the temperature of the run.[15]

(15) "International Critical Tables," Vol. III, McGraw-Hill Book Co., New York, N. Y., 1928, p. 27

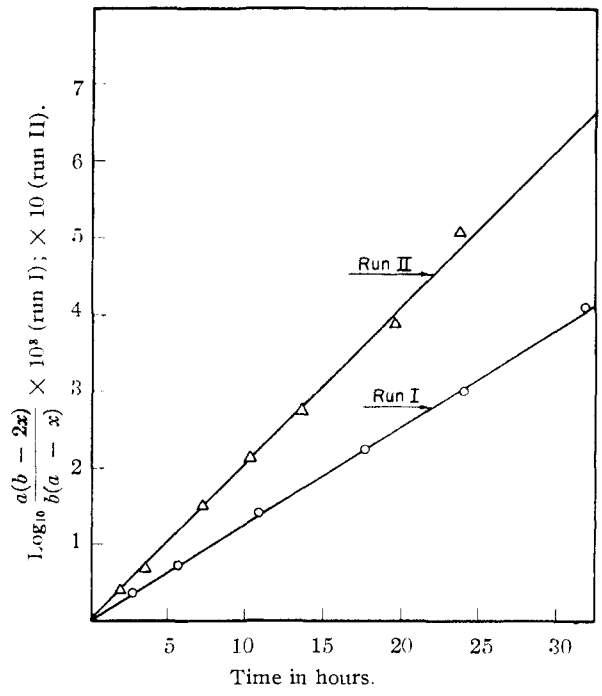


Fig. 2.—Reaction of α-chlorocodide with piperidine in benzene solution at 59.1°.

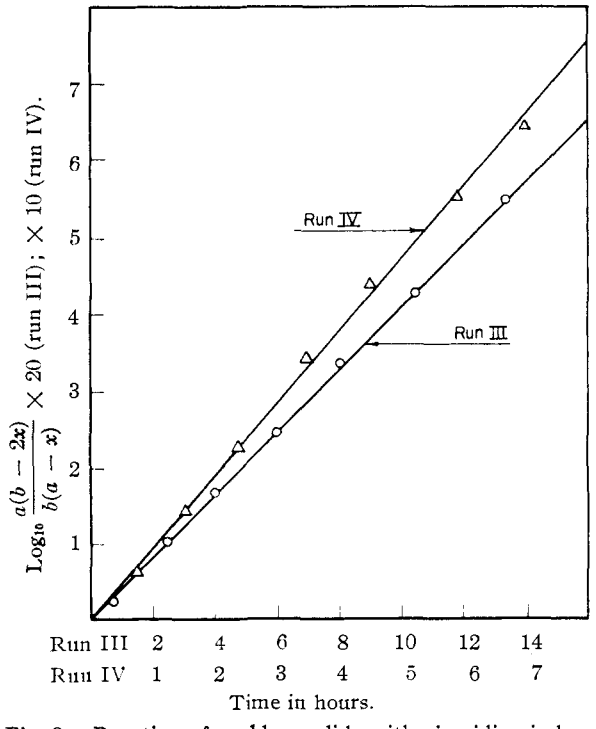


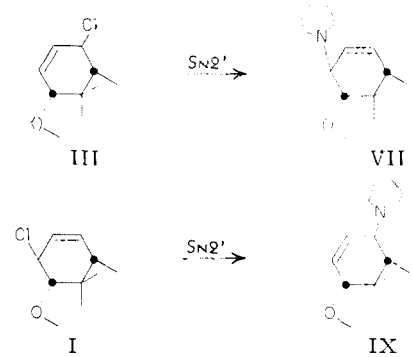
Fig. 3.—Reaction of α-chlorocodide with piperidine in benzene solution at 70.0°.

tion proceeds while the third-order rate "constant" k_3 shows a continuous increase with time. The second-order rate constant, on the other hand, shows no trend in any of the runs from 12 to 82% reaction and does not vary by more than the experimental error when the concentration of piperidine is doubled while maintaining the α-chlorocodide concentration substantially constant.

From the data it is possible to calculate the Arrhenius activation energy E = 14.0 ± 1.0 kcal./mole ($\log_{10}A$ = 5.14 at 70.0°) while the heat of activation H^+ = 13.3 ± 0.7 kcal./mole.[16a]

Conclusions

Unambiguous proof has now been provided that the reaction of α-chlorocodide with piperidine is an SN2′ reaction. This permits us to assign stereochemistry to 8-piperidocodide as shown in IX since both steric and electrical[11] factors require that the piperidine residue be on the same side of the ring as the original chlorine. Since the reaction of β-chlorocodide with piperidine is very much slower than that of α-chlorocodide and since it leads to the less stable isomer that reaction is obviously also SN2′. The reactions are illustrated below



We may now consider established the postulate[1] that those codeine (or morphine) derivatives with an unhindered back side (codeine, allopseudocodeine, codeine tosylate) undergo normal displacement with inversion and, except when the expected product is an easily rearranged unstable isomer (bromocodide and iodocodide from codeine tosylate) *without rearranagment.* Those compounds in which the back side is highly hindered (isocodeine, pseudocodeine, α-chlorocodide, β-chlorocodide, bromocodide and iodocodide) undergo bimolecular displacement with rearrangement (SN2′), the entering group being *cis* to the displaced group.[11]

The ease with which SN2′ displacements are observed with these substances is due to an unusual combination of factors. Highly inaccessible back side preventing SN2 reaction, the inductive effect of the C–O bond of the oxide ring which raises the energy of the allylic cation which would lead to SN1 reaction (*cf.* the well known sluggishness of β-halo ethers in SN1 processes) and, in the case of isocodeine and α-chlorocodide, the added driving force attending the transformation of the Δ^7-system to the more favorable Δ^6-arrangement.

An interesting feature of the reactions is that the departing halogen is pseudo equatorial and cannot take a pseudo axial conformation because of the geometric limitations imposed by the *trans* fused isoquinoline system. The transition state of these reactions is thus as we have discussed in the preceding paper[11] for simple cyclohexene derivatives, and in the halocodide cases hydrogen bonding may

(16) (a) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 95; (b) p. 101.

not be as important as in acyclic cases. As a matter of fact, SN2′ displacement is easily effected with ethyl mercaptide anion, for instance.[1]

Finally, it should be pointed out that the activation energy for the reaction of α-chlorocodide and piperidine is not unlike that of a number of simple SN2 reactions, while the value of log A is compatible with the rather stringent steric requirements for the reaction ($\log_{10} A$ is not unlike that found for some Diels–Alder reactions[16b]).

The work which we have just outlined provides final confirmation for the structure and stereochemistry of the displacement products of the halocodides, the stereochemistry of pseudocodeine and allopseudocodeine and, of course, of the corresponding morphine derivatives.[1]

Experimental

All melting points were determined with Anschütz thermometers in a stirred, electrically heated oil-bath.

α-Chlorocodide.—This was prepared either by the method of Wieland and Kappelmeier,[17] using thionyl chloride or by the phosphorus pentachloride procedure of Small and Cohen.[18a] The former method, using purified thionyl chloride gave 81% yield of α-chlorocodide, but the latter, although giving only 53% yield, was more convenient. The pure α-chlorocodide had m.p. 149–151° (reported m.p. 147–148°[18b]; 152–153°[18c]).

β-Chlorocodide.—The procedure used was that of Speyer and Rosenfeld[19] which involves heating α-chlorocodide in bromobenzene solution. The yield was 70% and the pure product (from alcohol) had m.p. 153–154° (reported[19] m.p. 153°).

Bromocodide.—The procedure of Schryver and Lees[20] gave 55% yield. The pure compound had m.p. 161–163° from alcohol (reported[20] m.p. 162°).

Iodocodide.—The procedure of Small and Cohen[18a] was used, but acetone was employed rather than methanol for the reaction of α-chlorocodide with sodium iodide, as a purer product was obtained in this way: α-chlorocodide (7.9 g.) was refluxed 7.5 hours with a solution of 7.6 g. of sodium iodide in 130 ml. of acetone. Working up as described and recrystallizing from acetone gave iodocodide as colorless crystals which sintered at 163° when introduced in the bath at 150° (reported[18a] m.p. 159–160°). It is interesting that while iodocodide sinters without melting, mixtures with α-chlorocodide melt to a clear liquid.

Lithium Aluminum Hydride Reductions. (a) **α-Chlorocodide.**—α-Chlorocodide (2.56 g.) was dissolved in 25 ml. of dry tetrahydrofuran and was added slowly to a solution of 0.88 g. of lithium aluminum hydride in 25 ml. of dry tetrahydrofuran. The mixture was refluxed for 48 hours under nitrogen and excess reducing agent was decomposed, with cooling, by addition of 6 ml. of ethyl acetate. The reaction mixture was poured into ice-water, 4 ml. of concentrated ammonia solution was added and the precipitated material was filtered with the aid of Super-Cel. The solid mixture, mixed with anhydrous sodium carbonate, was extracted with six 75-ml. portions of 1:1 chloroform–ether. The aqueous solution was also extracted with chloroform–ether after saturation with potassium chloride. The combined extracts were washed with 200 ml. of 2% potassium hydroxide solution and then with 200 ml. of saturated sodium chloride solution, and were evaporated to dryness *in vacuo*. The dark oily residue weighed 1.41 g. and showed no phenolic hydroxyl in the infrared.

The crude product was dissolved in 100 ml. of petroleum ether (b.p. 30–60°) and the solution was poured through a 4 × 1 cm. column of alumina. The eluate was concentrated to a small volume and gave on cooling 0.77 g. of nearly colorless crystals of Δ^6-desoxycodeine, m.p. 98–100° (reported[18a] m.p. 105–106°). No further crystalline material could be recovered from the column. The base was purified as its salicylate which was sublimed in high vacuum at 133–140° to give m.p. 194–196° (reported[21] m.p. 195–196°), and also as its anhydrous hydrochloride, m.p. 243–244°, prepared by adding a solution of anhydrous hydrogen chloride in dry ether to a dry ether solution of the base and recrystallizing the salt from butanone–cyclohexane. The hydrated form described by Small and Cohen[18a] could be prepared, but accurate determination of its melting point was difficult as it loses water on heating. The free base could be regenerated from the hydrochloride by addition of ammonia.

(b) **Bromocodide.**—In a similar manner, reduction of 1.91 g. of bromocodide gave 0.80 g. of crude oily product which was crystallized from petroleum ether (30–60°) to give 496 mg. of Δ^7-desoxycodeine, m.p. 81–82° (reported[4b] m.p. 82–83°). The melting point of the mixture with authentic Δ^7-desoxycodeine was kindly determined by Dr. Rapoport who found no depression. The hydrochloride of the base had m.p. 239.0–239.5° dec. after crystallization from butanone (reported 4[4b] m.p. 239–240°).

(c) **Iodocodide.**—In the same fashion 2.54 g. of iodocodide gave 0.35 g. of a dark red foam which was purified by passing its solution in 1:1 benzene–petroleum ether through a short column of alumina. The filtered ether solution of the product gave the hydrochloride of Δ^7-desoxycodeine, m.p. 235–236° (reported[4b] m.p. 239–240°; undepressed on mixing with authentic sample,[4b] but depressed by the hydrochloride of Δ^8-desoxycodeine) on treatment with anhydrous ethereal hydrogen chloride and recrystallization from butanone.

(d) **β-Chlorocodide.**—Similar reduction of 2.17 g. of β-chlorocodide led to 1.32 g. of a colorless oil which gave an infrared spectrum identical with that of the crude product obtained from bromocodide and lithium aluminum hydride. Crystallization from petroleum ether (30–60°) gave 0.95 g., m.p. 77–81°, which did not depress the melting point of Δ^7-desoxycodeine.

Displacements on Codeine Tosylate.—Codeine tosylate was prepared according to published procedures.[4a] The crude tosylate recrystallized from ether was obtained pure by passing its ether solution through a short column of alumina. It had m.p. 129–130° (reported m.p. 126–128°[4a]; 121–121.5°[4b]). It is changed into amorphous, ether-insoluble material, if recrystallization is conducted in methanol or mixtures containing methanol.

(a) **With Chloride Ion.**—A solution of 0.50 g. of codeine tosylate and 0.18 g. of lithium chloride in 20 ml. of acetone was refluxed under anhydrous conditions for four hours. The cooled solution was poured into 60 ml. of water and the resulting suspension was extracted with benzene. Drying over sodium sulfate and evaporation gave crystalline material which was recrystallized from alcohol to give 0.20 g. of α-chlorocodide, m.p. 151–154°. This did not depress the melting point of authentic α-chlorocodide.

(b) **With Bromide Ion.**—A solution of 0.245 g. of codeine tosylate and 0.31 g. of lithium bromide in 10 ml. of acetone was refluxed for 2.5 hours and was then worked up essentially as described above to give 0.192 g. (98%) of crude crystalline bromocodide, m.p. 153–159°. One recrystallization from ethanol gave material melting at 155–156°, undepressed after mixing with authentic bromocodide (m.p. 157–158°).

(c) **With Iodide Ion.**—A solution of 0.40 g. of codeine tosylate and 0.13 g. of sodium iodide was refluxed in 20 ml. of acetone for 2.5 hours. The solution was then cooled, filtered from precipitated sodium toluenesulfonate and evaporated to dryness under reduced pressure. The residue was taken up in boiling ligroin. A small amount of insoluble residue was centrifuged out, and cooling then gave 0.15 g. (43%) of yellowish crystals, sintering at 161° when introduced in the bath at 152°. The infrared spectrum of the crystalline material was identical with that of authentic iodocodide.

(d) **With Piperidine.**—A solution of 0.27 g. of codeine tosylate and 1.0 ml. of piperidine in 10 ml. of benzene was refluxed for 36 hours. The benzene solution was cooled and extracted three times with dilute hydrochloric acid. The aqueous solution was extracted once with ether and was then made alkaline with sodium hydroxide solution. The ether extracts from the basic solution were washed repeatedly

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with water, dried over anhydrous sodium carbonate and evaporated to yield 0.19 g. of crude 6-piperidocodide, completely soluble in 20–40° petroleum ether (codeine tosylate is insoluble in this solvent). A portion of the product (0.18 g.) was converted to its picrate (0.40 g.) which had m.p. 244° dec. after two recrystallizations from methanol–acetone. This was not depressed on mixing with the authentic picrate of 6-piperidocodide (see below).

6-Piperidocodide.—This base was prepared by the method of Small and Palmer[5] from bromocodide and piperidine. The pure base is difficult to obtain crystalline and is best characterized as its picrate obtained from alcohol as brilliant yellow crystals, m.p. 243.5–244° dec. when introduced into the bath at 212°. Three crystallizations from methanol raised the melting point to 247° dec.

Anal. Calcd. for $C_{35}H_{36}O_{16}N_8$: C, 50.97; H, 4.40. Found: C, 50.93; H, 4.48.

6-Piperidocodide was also prepared by heating β-chlorocodide and piperidine in an inert solvent. A solution of 0.40 g. of β-chlorocodide and 0.8 ml. of piperidine in 4 ml. of toluene was heated in a sealed tube at 100° for 250 hours. The calculated amount (0.16 g.) of piperidine hydrochloride was collected by filtration and the theoretical quantity (0.51 g.) of 6-piperidocodide, identified by its infrared spectrum, remained after removal of the solvent from the filtrate.

When a solution of 1.00 g. of β-chlorocodide and 2.2 ml. of piperidine in 20 ml. of benzene was refluxed 238 hours, only 50% of the theoretical amount of piperidine hydrochloride was formed and the product was a mixture of 6-piperidocodide and β-chlorocodide, as shown by its infrared spectrum. This result should be contrasted with the ease of formation of 8-piperidocodide.

8-Piperidocodide.—This was prepared by the procedure of Vongerichten and Müller[13] from α-chlorocodide and piperidine without solvent. The 8-piperidocodide so obtained (71%) had m.p. 114–116°.

This was also prepared in solution by refluxing a solution of 0.50 g. of α-chlorocodide and 0.6 ml. of piperidine in 10 ml. of benzene for six hours. The filtered benzene solution was washed twice with 5% aqueous sodium hydroxide solution, then repeatedly with water. The infrared spectrum of the residue from the evaporated benzene solution showed it to be nearly pure 8-piperidocodide. One crystallization from methanol gave 0.42 g. (73%) which had m.p. 113–117° after drying *in vacuo* for three hours. The melting point was not depressed on admixture with 8-piperidocodide prepared according to Vongerichten and Müller.[13] A 76% yield of 8-piperidocodide could also be obtained by refluxing 1.0 g. of α-chlorocodide and 1.2 ml. of piperidine in 10 ml. of acetone for two hours.

Kinetics. (a) α-Chlorocodide and Piperidine in Benzene Solution.—Pure α-chlorocodide was obtained as described earlier and was recrystallized several times from alcohol. The resulting crystals, dissolved in dry ether, were obtained colorless by passing their solution in anhydrous ether through a column of alumina. They had m.p. 151–153°.

Piperidine (Eastman Kodak Co., white label) was converted to the benzoyl derivative,[22] b.p. 165–170° (8 mm.). The benzoylpiperidine (211 g.) was stirred for four hours with 2.5 g. of powdered potassium permanganate in 1500 ml. of acetone and again distilled (b.p. 154–156° (5 mm.)). Base hydrolysis, etc., gave pure piperidine which was dried over potassium hydroxide and distilled over sodium. It had b.p. 104–106°. This purified piperidine was used in all kinetic runs.

The reactions were carried out by placing the piperidine, dissolved in dry benzene in a thin walled glass bulb contained in an outer tube in which the benzene solution of α-chlorocodide was introduced. The outer tube was sealed and mixing was accomplished after thermostatting to the desired temperature by breaking the inside bulb. The reaction was stopped by immersing in a Dry Ice–chloroform–carbon tetrachloride mixture. The water extracts from the material in the tube were then neutralized to phenolphthalein with 0.1 *N* acetic acid and the chloride ion was determined with 0.01 *N* silver nitrate, using dichlorofluorescein as indicator. The accuracy of the method used was checked with a known amount of piperidine hydrochloride in benzene solution under the same conditions used in the actual runs. The method was accurate to 0.5%. The calculations and results are presented in the Discussion section.

(b) **Codeine Tosylate and Piperidine in Toluene Solution.**—The procedure was the same as that described above. Codeine tosylate was prepared as mentioned earlier. The piperidine was purified as above. The piperidine consumed in a run was determined by titration with 0.02 *N* hydrochloric acid, using phenolphthalein as indicator. Rate constants k_2 and k_1 were calculated as in the chlorocodide case, assuming that two moles of piperidine is consumed for each mole of codeine tosylate utilized. Since, however, the reactions with codeine tosylate remain homogeneous, we also calculated k_2, on the assumption that only one mole of piperidine is used up for each mole of codeine tosylate which reacts. All concentrations were corrected for volume expansion of toluene at the temperature of the run. The results, shown in Table III, demonstrate the second-order nature of the reaction and k_2' seems to be a better constant than k_2. Because of the uncertainty attaching to the actual values of the rates, the activation energy was not calculated.

TABLE III

SUMMARY OF KINETIC RESULTS FOR THE REACTION OF CODEINE TOSYLATE WITH PIPERIDINE IN TOLUENE SOLUTION

a = concentration of codeine tosylate; b = concentration of piperidine.

Temp., °C. ± 0.01°	a, moles/l.	b, moles/l.	10^5k_2, l./mole. sec.	$10^5k_2'$, l./mole. sec.	10^5k_1, sec.$^{-1}$
73.86	0.0739	0.2057	6.5 ± 0.6	5.6 ± 0.3	1.02 ± 0.04
73.86	.0756	.0971	7.3 ± 1.0	5.1 ± .2	0.43 ± .03
84.67	.0819	.1157	16.5 ± 2.4	11.9 ± .7	11.8 ± .7
84.67	.0826	.2408	14.3 ±	12.4 ±	26.9 ±

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