[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Asymmetric Induction Studies with Optically Active Biphenyls. The Reactions of Phenylglyoxylates of the Phenyldihydrothebaine Series with Methylmagnesium Iodide[1]

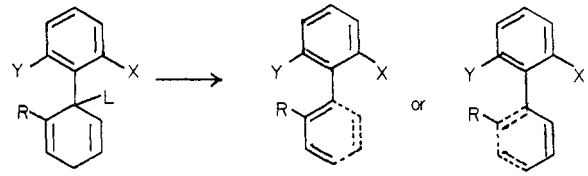
BY JEROME A. BERSON AND MICHAEL A. GREENBAUM

RECEIVED APRIL 22, 1957

The action of methylmagnesium iodide on the phenylglyoxylates of phenyldihydrothebaine, the corresponding isomethine, dihydroisomethine and bis-methine has been examined. (−)-Atrolactic acid is produced in exceptionally high optical yields. An explanation of the results is given in terms of conformational factors and compression effects.

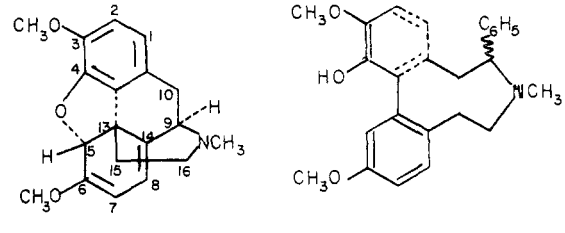
The reactions of Grignard reagents with α-ketoesters of optically active acyclic and alicyclic alcohols commonly result in asymmetric induction; one of the two possible diastereomeric tertiary α-hydroxyesters predominates in the product, and saponification of the mixture gives optically active α-hydroxyacid.[2] When the absolute configuration of the alcohol portion of the α-ketoester is known, the absolute configuration of the predominant enantiomer of the hydroxyacid can usually be predicted and, conversely, by the use of a hydroxyacid whose absolute configuration is known, that of the alcohol can be deduced.[2b,c] In connection with studies of absolute configuration and asymmetric induction in the biphenyl series, it was of interest to us to extend this type of reaction to derivatives of optically active 2-hydroxybiphenyls. It was anticipated that the results might help to clarify some aspects of the subtle interplay of forces at work in asymmetric induction reactions, and also might provide a basis for determining the absolute configurations of biphenyl derivatives. As a prerequisite for these studies, it was necessary to know the absolute configurations of some 2-hydroxybiphenyls.

The Absolute Configuration of the Biphenyl System in Phenyldihydrothebaine.[1b]—One of the possible operational bases for determining the absolute configuration of a biphenyl system is in the study of "asymmetric transfer" reactions of the type we have previously discussed.[3] In these cases, a hydroaromatic molecule with central asymmetry, *e.g.*, I, is converted by loss of a group at the asymmetric center to a fully aromatic biphenyl. Since such a reaction must choose between two diastereomeric, energetically non-equivalent transition states, that one of the two enantiomeric, axially asymmetric products (IIa or IIb) which is formed *via* the lower-energy transition state will predominate. The assignment of an absolute configuration to the biphenyl then requires (i) a knowledge of the absolute configuration of I and (ii) a decision on which of the two transition states is of lower energy. Satisfaction of both of these requirements clearly will not often be possible. However, the transformation of thebaine (III) to the phenyldihydrothebaines (IV) is a unique system in which the necessary decisions can be made with confidence.



IIa IIb

The absolute configuration of thebaine (III) has been established beyond question by several independent lines of evidence. Bentley and Cardwell[4] have shown that the changes in optical rotation of (−)-diacetylmorphothebaine with increasing solvent polarity related this substance to (−)-glaucine, which in turn had been related to (−)-alanine. Corrodi and Hardegger[5] have related C.9 of N-norapocodeine to D-(−)-aspartic acid by direct degradation, and Kalvoda, Buchsacher and Jeger[6] have degraded thebaine to (−)-*cis*-2-methyl-2-carboxycyclohexylacetic acid, the absolute configuration of which had been established.



III IV

Thebaine (III) reacts with phenylmagnesium bromide to give, after hydrolysis, a mixture of unequal amounts of two diastereomeric phenyldihydrothebaines (IV).[7] The major product, (+)-

(1) (a) This work was supported by a grant, G-1888, from the National Science Foundation. For preliminary reports see (b) J. A. Berson, THIS JOURNAL, **78**, 4170 (1956); (c) J. A. Berson and M. A. Greenbaum, *ibid.*, **79**, 2340 (1957).

(2) (a) A. McKenzie, *J. Chem. Soc.*, **85**, 1249 (1904), and many subsequent papers; (b) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); (c) V. Prelog, *Bull. soc. chim.*, 1087 (1956), and references therein cited; (d) D. A. Bovey, J. A. Reid and E. E. Turner, *J. Chem. Soc.*, 3227 (1951), and references therein cited; (e) for asymmetric inductions in other systems, see D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952), and subsequent papers by D. J. Cram and co-workers.

(3) (a) J. A. Berson and E. Brown, *ibid.*, **77**, 450 (1955); (b) for an alternative approach, see K. Mislow and P. Newman, *ibid.*, **79**, 1769 (1957).

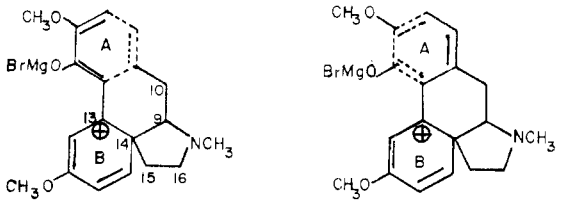
(4) K. W. Bentley and H. M. E. Cardwell, *J. Chem. Soc.*, 3252 (1955).

(5) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **38**, 2038 (1955).

(6) J. Kalvoda, P. Buchsacher and O. Jeger, *ibid.*, **38**, 1847 (1955).

(7) (a) M. Freund, *Ber.*, **33**, 3234 (1905); (b) L. Small, L. J. Sargent and J. A. Bralley, *J. Org. Chem.*, **12**, 1839 (1947); (c) R. Robinson, *Nature*, **160**, 815 (1947); (d) K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 947 (1952). For detailed reviews, see (e) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, pp. 272–288; (f) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, pp. 17–22; (g) H. L. Holmes and G. Stork in "The Alkaloids," Vol. II, edited by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1952, pp. 167–171, 197–198.

α-phenyldihydrothebaine, differs from its companion, the (+)-δ-isomer, only in the configuration at the asymmetric carbon, since destruction of this center in either molecule leads to optically active biphenyl derivatives of identical structure and configuration. Regardless of the details of the mechanism of formation of the phenyldihydrothebaines, the originally tetrahedral C.13 must become trigonal at or near the transition state for the migration of C.15 from C.13 to C.14. The two rings of the potential biphenyl system are forced to approach coaxiality, and the situation then becomes analogous to the reaction I → II. Scale molecular models clearly reveal that one of the two diastereomeric transition states thus produced is very much more stable than the other. The argument is most conveniently presented in terms of the metastable intermediates Va and Vb, but applies with equal force to the corresponding transition states.



Va Vb

In Va, the dihedral angle (θ) between the plane defined by C.15-C.14-C.9 and that defined by C.14-C.9-N is close to 0° (see Fig. 1) when the angle (ρ) between the planes of rings A and B is about 45°. This allows construction of the five-atom ring (C.15, C.14, C.9, N, C.16) without angle strain. As one ring of the potential biphenyl system is twisted with respect to the other about their common axis in the direction that will more rapidly achieve coplanarity (decreasing ρ), θ increases and Baeyer strain in the five-membered ring increases. The most favorable θ is probably slightly greater than 0°, since non-bonded interactions between adjacent ring hydrogens are diminished by a slight puckering of the five-membered ring.[8] When ρ reaches 15°, however, θ is about 60°, and the angle strain in the five-atom ring is very severe. (Actually, it cannot be constructed at all using Stuart–Briegleb models). In order for the potential biphenyl system to achieve the configuration Vb, ρ must reach and pass 0° and θ must become still larger than 60°. This puts intolerable strain in the five-atom ring and, further, requires severe distortion of the bond angles and distances in the C.9–C.10 ring and/or departures from coaxiality of rings A and B.

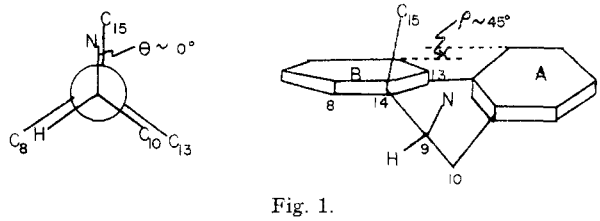


Fig. 1.

We conclude that the absolute configuration of the biphenyl system in (+)-α- and (+)-δ-phenyldihydrothebaines[7b] is that shown in IV, derived from Va, and that of the remaining isomers, (−)-α- and (−)-δ-, obtained[7b] by partial thermal racemization, is enantiomeric with that shown in IV.

The Reactions of Phenylglyoxylates of the Phenyldihydrothebaine Series with Methylmagnesium Iodide.—(+)-α-Phenyldihydrothebaine (IV) and the corresponding isomethine (VIa), dihydroisomethine (VIb) and bis-methine (VII) were prepared according to the directions of Small, Sargent and Bralley.[7b] All four of the phenols reacted readily with phenylglyoxylyl chloride in pyridine–ether at room temperature to give the corresponding phenylglyoxylates. The esters of the aminophenols (IV, VIa and VIb) were purified as the crystalline perchlorates to constant specific rotation and melting point. Since there are two sources of asymmetry in these molecules, any contaminant introduced by partial racemization of the biphenyl system would have been diastereomeric with the desired substance, and, consequently, achievement of chemical purity assured optical purity. The phenylglyoxylate of VII was crystalline and dextrorotatory. It is conceivable that this material might have been partially racemized, but the asymmetric induction experiment (*vide infra*) showed that the amount of (−)-isomer contaminant could not have exceeded 3.5%.

TABLE I

REACTIONS OF CH_3MgI WITH PHENYLGLYOXYLATES OF ROH

ROH	Mole ratio[a]	Atrolactic acid chemical yield, %	Atrolactic acid optical yield, [b]	Stereoselectivity[c]
IV	1.00	78	71	5.5
IV	1.25	67	70	5.7
VIa	1.25	70	91	21
VIb	1.25	63	89	17
VII	1.25	61	93	28

[a] Moles of CH_3MgI/moles of phenylglyoxylate. [b] Optical yield = 100 [specific rotation of atrolactic acid obtained/(−57°)]. [b]Rotations were measured in *M* aqueous sodium hydroxide to avoid the difficulty of concentration effects on the equilibrium between the acid and its anion. A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910), report $[\alpha]_D$ −57.0° for optically pure (−)-sodium atrolactate in water. [c] [Optical yield + ½(100 − optical yield)]/[½(100 − optical yield)].

The reactions of the phenylglyoxylates with methylmagnesium iodide were carried out in ether solution. "Inverse addition" of an accurately known quantity of the Grignard reagent to the solution of the ester was employed to minimize the formation of products other than the atrolactate. The Grignard reaction mixtures, after hydrolysis with ammonium chloride, were subjected to vigorous saponification, and the specific activity of the total acid fraction was determined. The results are given in Table I. In each case, (−)-atrolactic acid predominated.

Since the primary theoretical interest was in the direction and magnitude of the stereoselectivity of attack upon the keto carbonyl group, it was desir-

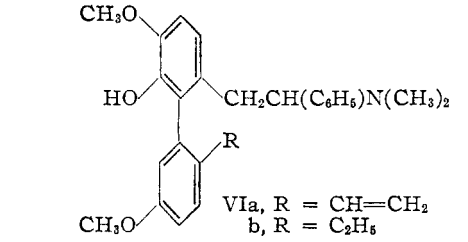
(8) Compare the dihedral angle of 17° in the pyrrolidine ring of hydroxyproline [J. Donohue and K. N. Trueblood, *Acta Cryst.*, **5**, 419 (1952)].

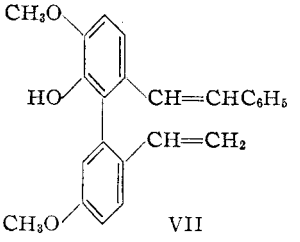
able to show that the observed optical activity arose during this attack and was not altered subsequently. In this system, there were three independent possible sources of artificial fractionation that might have led to an erroneous estimate of the stereoselectivity: (i) incomplete saponification of the mixture of diastereomeric atrolactates,[2b,9b] (ii) recrystallization of the atrolactic acid fraction[9a] and (iii) partial consumption of the atrolactates at unequal rates by attack of the Grignard reagent on the ester carbonyl group.[9c]

Since the acid fractions in all cases contained little or no phenylglyoxylic acid, it was unnecessary to perform any chemical purification, and type ii fractionation was avoided. The possibility of type i fractionation was eliminated for the case of IV (and, by assumption, for the rest of the cases, which were processed in the same manner) by a material balance. This was facilitated by the circumstance that IV is an aminophenol. With one mole of Grignard reagent, the phenylglyoxylate of IV gave, after saponification of the reaction mixture, 78% of atrolactic acid, 15% of neutral material (calculated as 1,1,2-trimethylphenylethylene glycol; however *vide infra*), 92% of phenyldihydrothebaine and less than 0.5% of unsaponified ester.

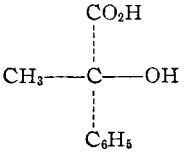
It was clear that regardless of the direction and efficiency of possible type iii fractionation, the magnitude of the optical and chemical yields of Table I demonstrated a high degree of asymmetric induction in the reaction of the keto group of the phenylglyoxylates. It was nevertheless of interest to investigate the extent to which the magnitude of the optical yield reflected the true stereoselectivity in this process. The problem of type iii fractionation has been considered for the case of 17β-androstanyl phenylglyoxylate by Prelog and co-workers.[9c] In this case, the products resulting from "normal addition" of the ester to methylmagnesium iodide were atrolactic acid, $[\alpha]_D$ +6.2°, and a neutral substance, presumably 1,1,2-trimethylphenylethylene glycol, $[\alpha]_D$ −0.64°. The methyl ester prepared from atrolactic acid of $[\alpha]_D$ +6.2° gave a glycol of $[\alpha]_D$ +4.0°. Fractionation was thus clearly demonstrated, the androstanyl ester of (−)-atrolactic acid reacting faster with excess Grignard reagent than did that of (+)-atrolactic acid. In our case, this type of demonstration did not appear to be feasible. The neutral material obtained from IV phenylglyoxylate and one mole of methylmagnesium iodide was chemically impure, which was not surprising, since it had been derived by "inverse addition." Further, on the assumption that Prelog's glycol of $[\alpha]_D$ +4.0° was of the same optical purity as atrolactic acid of $[\alpha]_D$ +6.2°, the $[\alpha]_D$ of optically pure 1,1,2-trimethylphenylethylene glycol is 24.3°. The neutral fraction from IV phenylglyoxylate had $[\alpha]_D$ +29.4°, suggesting the presence of a strongly dextrorotatory impurity. Also the alternative assumption that the neutral fraction was all glycol and the fact that it was dextrorotatory imply a high fractionation efficiency, which is in conflict with the result reported below. We conclude that no quantitative significance can be attached to the $[\alpha]_D$ of the neutral fraction in this case. That type iii fractionation was probably not important was suggested by a comparison (see Table I) of the results of reactions of IV phenylglyoxylate with 1.00 and with 1.25 moles of Grignard reagent. In the latter experiment, the chemical yield of atrolactic acid was lower, as anticipated, but the optical purity was identical within experimental error with that of the atrolactic acid obtained with 1.00 mole of Grignard reagent. Thus, despite the fact that an additional 13% of the atrolactic ester mixture presumably was consumed in reaction with excess Grignard reagent, no significant change in composition occurred. The optical yield (apparent stereoselectivity) in case IV therefore seems to be a fairly reliable index of the true stereoselectivity in the Grignard addition to the keto group. Similar experiments with VIa, VIb and VII were not carried out, so that the quantitative reliability of the data is uncertain. Nevertheless, regardless of possible type iii fractionation, the true stereoselectivities are again very high. Further, since the chemical yields of atrolactic acid are moderately high, a change in apparent stereoselectivity of 5.7 (case IV) to 28 (case VII) would require a very large difference in type iii fractionation efficiency if the two true stereoselectivities for attack on the keto group were the same. It therefore seems likely that these true stereoselectivities are greater for cases VIa, VIb and VII than for IV.

(−)-Atrolactic acid, the predominant isomer formed in these reactions, has the absolute configuration VIII.[9d] It is formed in the highest optical yields ever observed in reactions of α-keto-





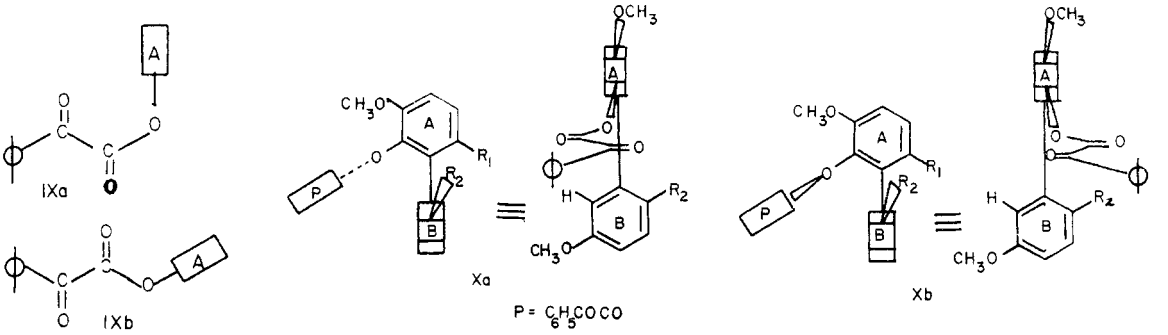
VII



VIII

esters with Grignard reagents. The direction and magnitude of the asymmetric syntheses seem to be entirely controlled by the existing asymmetry in the biphenyl system and not by the presence of an asymmetric carbon center, since destruction of the latter produces virtually no effect. (Compare the optical yields for VIa, VIb and VII.) A plausible (but by no means unequivocally established) physical interpretation of these results can be given in terms of shielding and compression effects. For the moment, assume that the most stable ground state conformation of the ketoester chain in the

(9) (a) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910); (b) A. McKenzie, *ibid.*, **89**, 365 (1906); (c) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta*, **36**, 325 (1953); (d) *cf.* J. H. Brewster, THIS JOURNAL, **78**, 4061 (1956).



phenyl glyoxylates is one in which the carbonyl groups are coplanar-transoid.[2b] The most stable disposition of this chain with respect to the biphenyl system is one in which the plane of the two keto groups is perpendicular to ring A and makes an angle of 60° with ring B (*cf.* X). Any rotation of the phenylglyoxylate chain about the ring A–ether O bond or about the ether O–ester carbonyl bond results in an increase in repulsion energy, due to compression of the chain against either the adjacent methoxyl or ring B. Actually, there are two coplanar-transoid conformations of the ketoester group, but one of these, IXa, is less stable than the other, IXb, because in IXa the keto oxygen is closer to ring A than is the ester carbonyl oxygen in IXb and, consequently, the repulsion energy is higher.

On theoretical grounds, it is likely that the major portion of the product is derived from the most stable ground state conformational isomers Xa and Xb. Curtin[10] has pointed out that if the rotational barriers separating ground state conformations are small compared to the over-all activation energies for chemical reaction, then the general premises of transition state theory imply that the proportions of products derived from the various ground state conformational isomers are, in principle, independent of the ground state population distribution. Nevertheless, the fortuitous set of circumstances existing in Grignard additions to α-ketoesters illustrated in Fig. 2 (a plot of free energy *vs.* a generalized conformational parameter, *e.g.*, angle of rotation) can result in a predominance of the product derived from the most stable ground state conformation, even if the rotational barriers are small. A is a stable conformation, U is an unstable one, $A^{\ddagger}$ is the transition state derived from A, and $U^{\ddagger}$ is that derived from U. If the product composition is kinetically controlled, the amounts of products from $A^{\ddagger}$ and $U^{\ddagger}$ (P_A and P_U, respectively) are in the relation $P_A/P_U = \exp(F_U^{\ddagger} - F_A^{\ddagger})/RT$. But also, $P_A/P_U = \exp(\Delta F_{AU}^{\ddagger} - \Delta F_A^{\ddagger})/RT$. Thus, unless there are particularly favorable circumstances associated with the formation of the transition states from unstable ground states, that is, unless the activation energies ($\Delta F_U^{\ddagger}$) are appreciably lower than those ($\Delta F_A^{\ddagger}$) required to raise the stable ground states to *their* transition states, the transition states derived from very unstable ground states can be ignored. In some cases, *e.g.*, E_2 reactions of cyclohexane derivatives, stereoelectronic or other factors can make $\Delta F_U^{\ddagger}$ much less than $\Delta F_A^{\ddagger}$. In the reactions of Grignard reagents with α-ketoesters, however, no such special circumstances exist; in fact, whatever differences there are in the reactions involving $\Delta F_U^{\ddagger}$ and $\Delta F_A^{\ddagger}$ usually operate to make $\Delta F_U^{\ddagger}$ greater than $\Delta F_A^{\ddagger}$. Thus, if $\Delta F_A^{\ddagger} \approx \Delta F_U^{\ddagger}$ and F_A is less than F_U by as little as 2 kcal./mole, the amount of product arising from $U^{\ddagger}$ at room temperature is negligible. This eliminates from consideration many conformations that represent rotational barrier maxima or metastable minima.

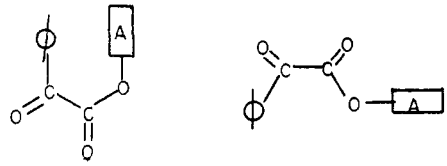
If the major portion of the product is derived from the most stable ground states of the starting material, only the four transition states derived from Xa and Xb need be considered. From Xa, the entering reagent may approach the keto carbon either from the direction of ring A, giving transition state XaA, or from the direction of ring B, giving transition state XaB. Likewise, Xb gives transition states XbA and XbB. The B transition states are very unstable, since approach in a direction perpendicular to the keto group is blocked by ring B. The choice now lies between XaA and XbA. In the approach to these two transition states, the shielding effects, exerted principally by the ring A methoxyl group, are identical. However, the compression effects, which come into play as the keto carbonyl begins to assume tetrahedral geometry, differ in that in XaA, the groups of the phenylglyoxylate chain, are compressed against hydrogen, whereas in XbA they are compressed against an alkyl group, R_2. Because of the unique geometry of the biphenyl system, the phenylglyoxylate chain is much closer to the groups it is being compressed against than in the acyclic and alicyclic cases, and the compression energy differences are much greater. XaA is more stable than XbA, and, consequently, the predominant product is (−)-atrolactic acid (VIII). Although the exceptionally high optical yields could not have been predicted, they are not unreasonable in retrospect. The proposed theory is consistent with the observation that the optical yield is higher with the phenylglyoxylates of VIa, VIb and VII than it is with that of IV. In the latter, the alkyl group (R_2 of X) is tied back in a ring. When the ring is broken, as in VIa, VIb and VII, the effective bulk of R_2 increases since it is now free to rotate, the free energy

(10) (a) D. Y. Curtin, *Rec. Chem. Prog.*, **15**, 111 (1954); (b) D. Y. Curtin and M. C. Crew, THIS JOURNAL, **77**, 354 (1955). The situation has been discussed further: (c) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); (d) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 44-47.

difference between XaA and XbA in increases, and the stereoselectivity increases.[11]

A number of alternative interpretations, involving restrictions of the conformational possibilities by chelate complexing, seem less likely at present than the one already given.

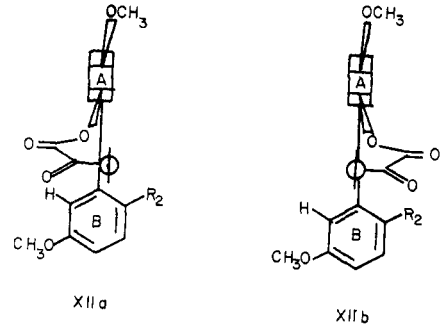
(i) If the two carbonyl groups are held coplanar-cisoid by such complexing with a single magnesium, conformations of the type XIa are much less stable than those of type XIb, for the same reasons that IXa is less stable than IXb. The product is then determined by the choice between XIIaA and XIIbA. That this choice is the determining factor



XIa XIb

is rendered very unlikely by the *a posteriori* but none the less powerful reasoning that XIIaA is the more stable transition state and it would lead to a predominance of (+)-atrolactic acid rather than to the observed predominance of the (−)-isomer.

(ii) If the two carbonyl groups are coplanar-transoid and held roughly coplanar with ring A by complexing of the ester carbonyl oxygen with the ring A methoxyl (XIII), the product is determined



XIIa XIIb

by the preference of the entering reagent for approach from the side of R_2 *vs.* approach from the side of H. If this preference is controlled by compression effects, approach from the side of R_2 would be favored, and (−)-atrolactic acid would be obtained. We are engaged in studying simpler 2-hydroxybiphenyl systems that lack the *o*-methoxyl group in order to check this point.

(iii) Conformation XIV, in which each carbonyl group is complexed with a methoxyl group, and the plane of the -COCO- residue is perpendicular to ring A and parallel to ring B would also lead to (−)-atrolactic acid. However, in order to explain

(11) In the change of IV to VIa, VIb and VII, the interplanar angle between the benzene rings of the biphenyl system may also be changed. This will result in altered effective sizes for H and R_2. The magnitude of this effect cannot now be estimated, but it is obviously insufficient to cause qualitative reversal of the *order* of effective sizes, since the direction of asymmetric induction is the same in all four cases. We recognize that the rotational barrier between Xa and Xb is very high, and may be comparable in magnitude to the activation energy for the Grignard addition. This does not qualitatively change the conclusions, since the product proportions are then controlled by the ground state population distribution, and Xa is more stable than Xb.

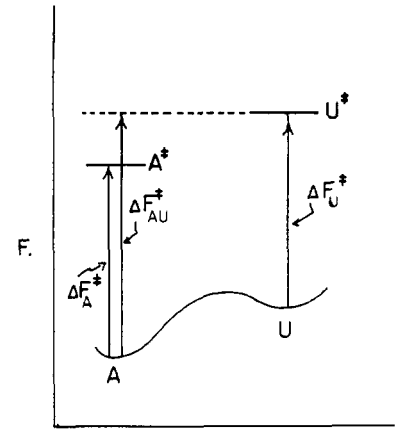
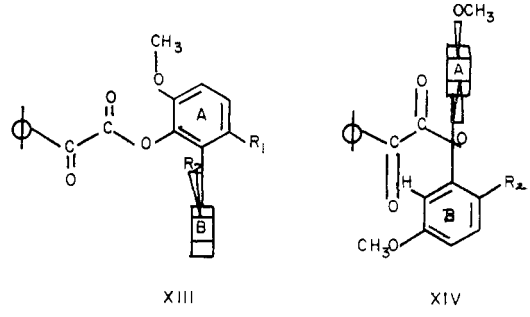


Fig. 2.

the fact that the stereoselectivity with the phenylglyoxylate of IV is 3–5 times less than with those of VIa, VIb and VII, it is necessary to assume that the degree of complexing is less in the former case. There is no obvious reason why this should be so, and, at present, this explanation seems unlikely. Experiments with simpler biphenyls are expected to bear on this point.



XIII XIV

Experimental[12]

(+)-α-Phenyldihydrothebaine (IV) was prepared by the action of phenylmagnesium bromide on thebaine. The substance was purified by direct recrystallization of the perchlorate from 95% ethanol, rather than by the previously reported procedure[7b] involving recrystallization of the hydrochloride. (The latter procedure is probably preferable for large scale runs, since recrystallization of the sparingly soluble perchlorate requires large volumes of solvent). The perchlorate had m.p. 247–248° dec., $[\alpha]^{32}D$ +39° (*c* 0.21 in 95% ethanol), $[\alpha]^{32}D$ +8.6° (*c* 0.94 in acetone); reported[7b] m.p. 248° dec., $[\alpha]^{26}D$ +35° (ethanol), $[\alpha]^{32}D$ +8.6° (*c* 0.94 in acetone); reported[7b] m.p. 248° dec., $[\alpha]^{26}D$ +35° (ethanol), $[\alpha]^{20}D$ +8.2° (acetone). The **methiodide** had m.p. 215–218°, $[\alpha]^{29}D$ +43.5° (*c* 0.40 in ethanol, *l* 4); reported[7b] m.p. 216.5–218°, $[\alpha]^{26}D$ +42.7° (in ethanol).

(+)-α-Phenyldihydrothebaine Phenylglyoxylate.—A solution of 0.035 mole of (+)-α-phenyldihydrothebaine was prepared by shaking 16.5 g. of the pure perchlorate with 100 ml. of concentrated ammonia water and 150 ml. of ether until all the solid dissolved. The ether layer was dried over sodium sulfate, filtered and treated with 50 ml. of dry pyridine and then 5.7 g. (0.035 mole) of phenylglyoxylyl chloride[13] (b.p. 90–91° (27 mm.), reported[13] b.p. 91° (9.5 mm.), reported[14] b.p. 125° (9 mm.)) in 25 ml. of

(12) Melting points are corrected. The analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, 4763 W. Adams Blvd., Los Angeles 16, Calif.

(13) M. S. Kharasch, S. S. Kane and H. C. Brown, THIS JOURNAL, **64**, 333 (1942).

(14) S. F. Acree, *Am. Chem. J.*, **50**, 389 (1913).

dry ether.[15] Pyridine hydrochloride precipitated immediately and heat was evolved. After 18 hours, the reaction mixture was poured into cold water, and the deep red ether layer was separated. The aqueous layer was made strongly basic with concentrated ammonia water and extracted with three 100-ml. portions of ether. These extracts were combined with the original ether layer, and the whole was extracted with 50 ml. of 2.5 *M* sodium hydroxide to remove unreacted phenol. The resulting pale yellow ether solution was washed with water, dried over sodium sulfate and evaporated *in vacuo*, leaving a yellow oil which still contained some pyridine. The oil was triturated with water, dissolved in a little ether, dried over sodium sulfate and the solution treated with 95% ethanol and an excess of 70% perchloric acid. The precipitated salt was filtered, washed with ethanol and ether and dried to give 19.0 g. (90% yield) of nearly pure **perchlorate**, m.p. 288–290 dec. (in a sealed capillary), $[\alpha]^{31}D$ +5.9° (*c* 0.50 in 95% ethanol, *l* 4). Recrystallization from ethanol gave fine white leaves, m.p. 295–296° dec., $[\alpha]^{31}D$ +6.8° (*c* 0.48 in 95% ethanol, *l* 4), $[\alpha]^{30}D$ +5.7° (*c* 1.00 in acetone, *l* 4). The infrared spectrum of the free base showed the expected ester and keto bands.

Anal. Calcd. for $C_{33}H_{32}O_9NCl$: C, 65.27; H, 5.14; Cl, 5.71. Found: C, 64.95; H, 4.80; Cl, 5.66.

(+)-α-**Phenyldihydrothebaine isomethine (VIa)**, prepared by Hofmann degradation of the methiodide of IV,[7b] had m.p. 101–102°, $[\alpha]^{30.5}D$ −281° (in ethanol); reported[7b] m.p. 101°, $[\alpha]^{20}D$ −280° (in ethanol). **The perchlorate** had m.p. 112–116°, $[\alpha]^{30}D$ −198° (in ethanol); reported[7b] m.p. 111–117°, $[\alpha]^{25}D$ −197° (in ethanol). **The isomethine methiodide** had m.p. 102–108° (from 25% ethanol), $[\alpha]^{30}D$ −208.5° (*c* 1.5 in ethanol, *l* 4); reported[7b] m.p. 100–110°, $[\alpha]^{25}D$ −207°. **The phenylglyoxylate** was prepared by the same procedure used for (+)-α-phenyldihydrothebaine phenylglyoxylate. It was obtained in 66% yield as the **perchlorate**, which had m.p. 151–152° (from absolute ethanol), $[\alpha]^{30}D$ −58.8° (*c* 1.05 in 95% ethanol, *l* 4). The molecular weight was determined by quantitative hydrogenation of the double bond in water over 5% palladium–charcoal.

Anal. Calcd. for $C_{34}H_{33}O_5N \cdot HClO_4$: C, 64.25; H, 5.35; N, 2.20; mol. wt., 636.1. Found: C, 64.47; H, 5.62; N, 2.13; mol. wt., 624.

(+)-α-**Phenyldihydrothebaine dihydroisomethine (VIb)** prepared by hydrogenation of VIa[7b] had m.p. 71–72°, $[\alpha]^{31}D$ −177° (in ethanol); reported[7b] m.p. 70–72°, $[\alpha]^{20}D$ −175° (in ethanol). The phenylglyoxylate, prepared from VIb and phenylglyoxylyl chloride as above, was obtained in 74% yield as the **perchlorate**, m.p. 184–185°, $[\alpha]^{30}D$ −27.8° (*c* 1.00 in ethanol, *l* 4). For comparison purposes, it also was prepared by catalytic hydrogenation of the isomethine phenylglyoxylate perchlorate in water at 24.5° and 760 mm. over 5% palladium–charcoal (see above). The clear aqueous solution obtained by filtering off the catalyst was diluted with five volumes of 95% ethanol and the whole concentrated *in vacuo* to a small volume. The solution was cooled and the precipitated white plates were dried to give the dihydroisomethine phenylglyoxylate perchlorate, m.p. 184–185°, $[\alpha]^{31}D$ −28.0° (*c* 1.04 in ethanol, *l* 4).

Anal. Calcd. for $C_{34}H_{35}O_5N \cdot HClO_4$: C, 64.05; H, 5.65; N, 2.20. Found: C, 64.32; H, 5.90; N, 2.10.

(+)-α-**Phenyldihydrothebaine bis-methine (VII)** was prepared by Hofmann degradation of the methiodide of the isomethine. The substance had m.p. 148–149°, $[\alpha]^{29}$ +46.0° (*c* 0.5 in ethyl acetate); reported[7b] for "(+)-vinylphenyldihydrothebaol" m.p. 149.5–150°, $[\alpha]^{25}D$ +47.1°. The **phenylglyoxylate**, prepared in 62% yield by the usual procedure, had m.p. 62–63.5° from ether–hexane, $[\alpha]^{30}D$ +28.4° (*c* 0.75 in ethanol, *l* 4). The molecular weight was determined by quantitative hydrogenation of both double bonds over 5% palladium–charcoal in ethyl acetate.

Anal. Calcd. for $C_{32}H_{26}O_5$: C, 78.37; H, 5.31; mol. wt., 490.5. Found: C, 78.41; H, 5.21; mol. wt., 489.5.

Reaction of Methylmagnesium Iodide with the Phenylglyoxylates. General Procedure.—The phenylglyoxylate (regenerated from the corresponding pure perchlorate with ammonia water in the cases of IV, VIa and VIb) in anhydrous ether (0.018–0.024 mole in 150 ml.) was treated with a *M* solution of methylmagnesium iodide in anhydrous ether. The amount of Grignard reagent used was 25% more than the amount calculated as necessary to react with one carbonyl group. An aliquot of the Grignard solution was titrated against standard hydrochloric acid before use. The reactions were carried out in a dry atmosphere under nitrogen. The Grignard solution was added over a period of 30 minutes in ten equal successive portions with vigorous stirring. The reaction mixture, after being heated at reflux an additional 30 minutes, was treated with saturated ammonium chloride solution. The ether layer was separated and washed with 10% sodium carbonate and water. After being dried over sodium sulfate, the ether was removed *in vacuo* and the resulting colorless or pale yellow oil was saponified with boiling 20% ethanolic potassium hydroxide for 4 hours. The solution was cooled, diluted with three volumes of water, washed with three 75-ml. portions of ether, and the aqueous layer was strongly acidified with hydrochloric acid. In the cases of the basic substances (IV, VIa and VIb), the atrolactic acid was extracted directly from the acidified mixture, the amine remaining in the aqueous layer. In the case of VII, the acidified solution was extracted with ether, the ether solution extracted with bicarbonate, the aqueous extract acidified and extracted with ether. After being dried over sodium sulfate, the ether solution was evaporated *in vacuo*, the residue was dried for 18 hours in a vacuum desiccator over calcium chloride and paraffin wax and examined polarimetrically. The residues did not appear to contain appreciable quantities of phenylglyoxylic acid, since they were colorless and did not give precipitates with 2,4-dinitrophenylhydrazine.

The properties of the crude atrolactic acids thus obtained were: from IV, $[\alpha]^{30}D$ −39.7° (*c* 8.8, *l* 4) (semi-solid); from VIa, $[\alpha]^{30}D$ −51.8° (*c* 6.4, *l* 4), m.p. 108–113°; from VIb, $[\alpha]^{29}D$ −50.8° (*c* 6.8, *l* 4), m.p. 108–112°; from VII, $[\alpha]^{29}D$ −53.1° (*c* 7.0, *l* 4), m.p. 109–112° (all rotations in *M* aqueous sodium hydroxide). Optically pure atrolactic acid has m.p. 115–116°.[9a]

Reaction of Methylmagnesium Iodide with the Phenylglyoxylate of IV. 1:1 Molar Ratio.—A solution of 0.30 mole of the phenylglyoxylate of IV (from 19.0 g. of the pure perchlorate) in 400 ml. of dry ether was treated with 38 ml. of 0.80 *M* methylmagnesium iodide in ether according to the procedure described above. The reaction mixture was worked up and saponified as above, the ethanolic solution was concentrated to a volume of 60 ml., cooled, and diluted with 250 ml. of cold water. The mixture was extracted with three 50-ml. portions of ether to give an ether layer (A-1), containing neutral material and unsaponified ester, and an aqueous layer (S-1). S-1 was acidified with 5 *N* hydrochloric acid and extracted with four 100-ml. portions of ether to give an ether layer (C), containing carboxylic acids, and an aqueous layer (S-2). (C) was extracted with 10% sodium bicarbonate, the bicarbonate extract acidified and extracted with ether to give an ether layer (D), containing only carboxylic acids. S-2 was neutralized with sodium bicarbonate and extracted with ether to give an ether layer (E), containing aminophenol (phenyldihydrothebaine). A-1 was extracted with cold *N* hydrochloric acid to remove basic material (unhydrolyzed ester), giving an ether layer (A-2), containing only neutral material, and an aqueous layer, which was neutralized and extracted with ether. This ether layer (A-3) contained unsaponified ester. The ether extracts were each washed with water, dried over sodium sulfate and evaporated. The neutral fraction (A-2) gave 0.75 g. of a reddish oil, $[\alpha]D$ +29.4° (*c* 1.60 in ethanol, *l* 4). The unsaponified ester fraction (A-3) gave less than 0.1 g. of dark residue. The aminophenol fraction (E) gave 11.0 g. of a purple glass. The carboxylic acid fraction (D) gave a faintly yellow solid which, after being dried to constant weight, amounted to 3.90 g., m.p. 89–95°, $[\alpha]^{29}D$ −40.6° (*c* 0.40 in *M* sodium hydroxide, *l* 4). The color indicated the presence of a trace

(15) Since there is a discrepancy between the boiling points recorded in the literature for phenylglyoxylyl chloride and since the boiling point of our material did not agree with either of these, we checked the identity of our sample by preparation of phenylglyoxamide. A solution of 8.5 g. of phenylglyoxylyl chloride in 50 ml. of dry ether was treated with gaseous ammonia. The precipitate was filtered off and the filtrate retreated as above. The ether was evaporated and the residue was combined with the first crop of material, washed with water and dried to give 7.3 g. (97%) of phenylglyoxamide, m.p. 88–90°. Recrystallization from water gave material melting at 91–91.5°, reported[16] m.p. 90–91°.

(16) L. Claisen, *Ber.*, **10**, 1664 (1877).

of phenylglyoxylic acid, although the quantity must have been very small since no precipitate was obtained when an ethanolic solution of the acid material was treated with Brady reagent. A trial experiment showed that even a very dilute solution of phenylglyoxylic acid produced a strong positive Brady test.

Acknowledgment.—We are indebted to the National Science Foundation for financial support, and the New York Quinine and Chemical Works for a generous gift of thebaine.

LOS ANGELES 7, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & CO.]

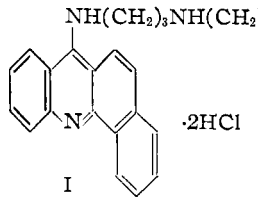
Synthetic Amebicides. IV. [(Benz[c]acridin-7-ylamino)-alkylamino]-alkanols and their Esters[1]

BY EDWARD F. ELSLAGER, FRANKLIN W. SHORT, MARIE JO SULLIVAN AND FRANK H. TENDICK

RECEIVED AUGUST 26, 1957

A group of [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols have been prepared by allowing 7-chlorobenz[c]acridine to react with the appropriate aminoalkylaminoalkanol. Condensation of various [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols with aliphatic acid chlorides or succinic anhydride yielded the corresponding [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol esters. Many of these heterocyclic alkanols and esters were highly active against *Endamoeba histolytica in vitro*, against experimentally-induced intestinal amebiasis in rats and dogs, and against amebic hepatitis in hamsters.

In previous communications,[1,2] it was reported that 7-(3-octylaminopropylamino)-benz[c]acridine dihydrochloride (PAA-2056) (I) and certain other 7-aminobenz[c]acridines are highly effective against *Endamoeba histolytica in vitro*, against intestinal amebiasis in rats and dogs, and against amebic hepatitis in hamsters. The present communication describes the synthesis of various [(benz[c]-



I

acridin-7-ylamino)-alkylamino]-alkanols and their esters, whose structures are indicated by formulas IV through VIII, where X and Y represent divalent alkyl groups, R a hydrogen, alkyl or hydroxyalkyl substituent and R′ an alkyl radical.

The [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols of type V (Table I) were synthesized by heating a mixture of the appropriate aminoalkylaminoalkanol, 7-chlorobenz[c]acridine[1] and phenol at 80 to 130° for 2 to 3 hours. Procedures employed in these laboratories for the preparation of 2-[2-(benz[c]acridin-7-ylamino)-ethylamino]-ethanol and 2-[3-(benz[c]acridin-7-ylamino)-propylamino]-ethanol have been reported previously.[3] A benz[c]acridine analog (II) of the anthelmintic and antiprotozoan drug Acranil[4] (IIIa) and the antibacterial and antirickettsial agent Entozon[5] (IIIb) was prepared in a similar manner from 7-chlorobenz[c]acridine and 1-amino-3-diethylamino-2-propanol.[6] Many of the intermediate aminoalkylaminoalkanols are commercially available or were generously supplied by other laboratories.[7-9] 2-[(5-Aminopentyl)-ethylamino]-ethanol was prepared from N-(5-bromopentyl)-phthalimide[10] by acid hydrolysis of the intermediate N-{5-[ethyl-(2-hydroxyethyl)-amino]-pentyl}-phthalimide. 2-[(3-Aminopropyl)-ethylamino]-ethanol,[11] 2-[(3-aminopropyl)-pentylamino]-ethanol and 1-(3-aminopropyl)-3-piperidinol were prepared by catalytic hydrogenation of the corresponding nitriles in the presence of Raney nickel or Raney cobalt catalyst.

[(Benz[c]acridin-7-ylamino)-alkylamino]-alkanol esters of type IV (Table II) and [(benz[c]-acridin-7-ylamino)-alkylimino]-dialkanol esters of structure VII (Table II) were prepared by stirring a suspension of the anhydrous [(benz[c]-acridin-7-ylamino)-alkylamino]-alkanol dihydrochloride or [(benz[c]acridin-7-ylamino)-alkylimino]-dialkanol dihydrochloride with an excess of the appropriate acid chloride on the steam-bath for 7 to 24 hours. The synthesis of the [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol monosuccinate esters (VI) (Table II) was accomplished by heating approximately molar equivalents of the anhydrous [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol dihydrochloride and succinic anhydride at 100–150° for 20 to 24 hours. The 2-{[3-(benz[c]-acridin-7-ylamino)-propyl]-ethylamino}-ethanol, diester with succinic acid, tetrahydro-

(1) For previous paper in this series, see F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan and F. H. Tendick, THIS JOURNAL, **80**, 223 (1957).

(2) (a) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan and F. H. Tendick, *ibid.*, **79**, 4699 (1957); (b) P. E. Thompson, D. A. McCarthy, J. W. Reinertson, A. Bayles and H. Najarian, *Antibiotics and Chemotherapy*, **7**, in press (1957).

(3) E. F. Elslager, E. L. Benton, F. W. Short and F. H. Tendick, THIS JOURNAL, **78**, 3453 (1956).

(4) F. Mietzsch and H. Mauss, German Patent 553,072 (1930) and U. S. Patent 2,113,357 (1938).

(5) Final Report 766, British Intelligence Objectives Sub-Committee (1946), H. M. Stationery Office, London.

(6) Purchased from the Eastman Kodak Co., Rochester 3, N. Y.

(7) The authors are indebted to Dr. Franklin Johnston and Dr. G. W. Fowler of the Union Carbide Chemical Co., South Charleston 3, W. Va., for the samples of 2-(2-aminoethylamino)-ethanol, 2-(3-aminopropylamino)-ethanol, 2-(2-amino-1-methylethylamino)-ethanol and 4-(3-aminopropylamino)-2-butanol.

(8) 2,2-(3-Aminopropylimino)-diethanol was obtained from the American Cyanamid Co., New York 20, N. Y.

(9) 2-[(4-Aminopentyl)-ethylamino]-ethanol and 2,2′-(4-aminopentylimino)-diethanol were obtained through the courtesy of Dr. C. M. Suter and Mr. B. F. Tullar of the Sterling-Winthrop Research Institute, Rensselaer, N. Y.

(10) W. Dirscherl and F. W. Weingarten, *Ann.*, **574**, 131 (1951).

(11) (a) J. H. Burckhalter, E. M. Jones, W. F. Holcomb and L. A. Sweet, THIS JOURNAL, **65**, 2012 (1943); (b) A. R. Surrey and H. F. Hammer, *ibid.*, **72**, 1814 (1950).