reflux under nitrogen for 90 min. The nearly colorless solution was cooled to room temperature and then poured into ice–water. The mixture was extracted with methylene chloride and the methylene chloride extracts were washed with water followed by 5% hydrochloric acid solution (three 100-ml portions) and saturated salt solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded a crystalline residue whose infrared spectrum was identical with that of **14b**. Recrystallization from acetone gave 0.70 g of colorless crystalline material which was identical with **14b** (melting point, mixture melting point, and infrared spectrum).

The Conformational Preferences in Diastereomers. I

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Nmr data are reported for a series of diastereomers involving a substituted phenylethyl skeleton. When the alkyl groups substituted at each asymmetric center are small, *i.e.*, methyl, both *gauche* and *trans* rotamers have substantial populations. When the alkyl groups are large, *i.e.*, isopropyl, these groups strongly prefer a *trans* orientation which allows the vicinal protons to be *trans* in the *erythro* but *gauche* in the *threo* isomer. In all cases but one, the *erythro* isomer exhibits the larger vicinal coupling constant.

The study of the mechanism of certain reactions involving *erythro* and *threo* pairs of diastereomers frequently has involved attempts to predict conformational preferences of each diastereomer.[1-3] These attempts frequently utilize molecular models to aid in deciding which rotamer was the most stable.

In other cases conformational preferences were decided from Newman projections. In simplified terms, the most stable rotamer was taken as the one in which nonbonded repulsions were minimized.[1,4-6] *gauche* interactions between large groups were considered particularly unfavorable.

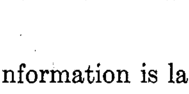
Although these ideas were logical and their application was fairly straightforward, they frequently were not based on physical or chemical evidence.

In recent years, nmr spectral evidence has been used to determine conformational preferences. Originally the main interest was in sugars and other cyclic molecules,[7,8] but more recently acyclic molecules have been investigated.[9-14]

In diastereomers which contain a proton at each asymmetric center, the vicinal coupling constant, J, should give an indication of the preferred conformation of the molecule. Unfortunately, the frequency of rotation about the central carbon is large compared to the nmr frequency separations between the vicinal protons,[15] and the vicinal coupling constant is a weighted average derived from contributions from several conformations. Nevertheless, a knowledge of the average conformation is still valuable, particularly where other information is lacking. Thus, if the vicinal protons are *trans* to one another, a coupling constant approaching 10–12 cps might be expected. If the vicinal protons are *gauche*, a coupling constant of 1–3 cps will be found. A mixture of *trans* and *gauche* conformers will give rise to intermediate values of J. A freely rotating structure such as an ethyl group, which presumably has no conformational preferences, often exhibit vicinal coupling constants of 6–7 cps.[15]

Electronegative groups substituted at the asymmetric centers will give rise to slightly lower values for J.[13,16] Snyder has recently shown that vicinal coupling constants vary with concentration of substrate[17] and type of solvent as much as ±1 cps; thus it probably is not worthwhile trying to interpret small differences in J values.

It seemed worthwhile to determine the effect of systematically increasing the hindrance at each asymmetric center on the conformational preferences of a set of diastereomers of the same basic skeleton, given in the formula. In this study, R_A and R_D were varied



$$R_A-\overset{H_B}{\underset{OH}{C}}-\overset{C_6H_5}{\underset{H_C}{C}}-R_D$$

from methyl to isopropyl; the data concerning the relevant chemical shifts, the coupling constants, and the multiplicity of peaks are given in Table I. The spectra were relatively easy to interpret. The most deshielded alkyl proton is almost certainly H_B, while H_C (also considerably deshielded by phenyl) was also usually far removed from the resonance absorptions of the remainder of the molecule. The vicinal coupling constant J_{BC} could usually be determined by inspection. Spin decoupling was utilized in cases where ambiguity existed. The individual compounds are discussed below.

In *erythro*-3-phenyl-2-butanol (I) (R_A, R_D = CH_3), both proton B and proton C are quintets. Thus the R_A–H_B coupling constant and the H_B–H_C coupling constant are very similar, namely *ca.* 7 cps; proton B basically sees a sum of four magnetically similar protons, giving a quintet pattern. Considering the

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(2) D. J. Cram, C. H. DePuy, and F. D. Greene, *J. Am. Chem. Soc.*, **70**, 790 (1958).

(3) (a) C. Kingsbury and D. J. Cram, *ibid.*, **82**, 1810 (1960); (b) H. C. Brown, K. Morgan, and F. Chloupek, *ibid.*, **87**, 2137 (1965).

(4) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 23, 159.

(5) J. L. Mateos and D. J. Cram, *J. Am. Chem. Soc.*, **81**, 2756 (1959).

(6) M. S. Newman, *J. Chem. Educ.*, **32**, 344 (1955).

(7) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).

(8) F. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962).

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(13) A. A. Bothner-By, *J. Am. Chem. Soc.*, **84**, 743 (1962).

(14) F. Anet, *ibid.*, **84**, 742 (1962).

(15) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Inc., New York, N. Y., 1959, p 101.

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(17) E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963).

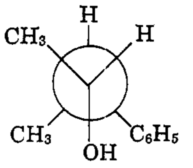
Table I[a]

	R_A	R_D	Coupling constants, cps J_{BC}	 J_{AB}	Chemical shift, ppm (multiplicity) A	 B	 C	 D
erythro-I	CH_3	CH_3	6.7	6.5	0.93 (2)[b]	3.74 (5)	2.58 (5)	1.22 (2)[b]
threo-I	CH_3	CH_3	6.3	6.3	1.08 (2)[b]	3.68 (5)	2.61 (5)	1.22 (2)[b]
erythro-II	CH_3	C_2H_5	6.7	6.5	0.99 (2)	3.83 (5)	2.46 (2 × 3)	
threo-II	CH_3	C_2H_5	6.0	6.0	1.09 (2)	3.75 (5)	2.34 (2 × 3)	
erythro-III	C_2H_5	C_2H_5	7.3[b]	3.2[b]		3.45 (3 × 2)		
erythro-IV	$(CH_3)_2CH$	$(CH_3)_2CH$	10.3[b,c] 10.2[d] 9.5[e]	1.6[b,c]		3.87 (2 × 2)		
threo-IV	$(CH_3)_2CH$	$(CH_3)_2CH$	3.6[b,c] 3.6[f]	7.6[b,c] 8.4[f]		3.58 (2 × 2)		
erythro-V[a]	CH_3	CH_3	4.0	6.4	1.13	3.76 (3 × 2)		0.78
threo-V[g]	CH_3	CH_3	6.5	6.5	1.07	3.65 (5)		0.69
erythro-VI	C_6H_5	D	8.4			4.73		2.88
threo-VI	C_6H_5	D	4.9			4.67		2.84

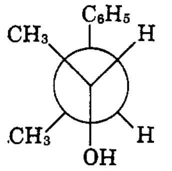
[a] Spectra were run in a Varian HR-60, in CCl_4 *ca.* 2.0 *M* in substrate. [b] Verified by spin decoupling. [c] At normal probe temperature, *ca.* +35°. [d] At 50°. [e] At 100°. [f] At −30°. [g] Cyclohexyl instead of phenyl substituted at C.

methyl group (A) only, there are no conformational preferences since all rotamers have the same energy. Rapid interchange of conformers leads to the "averaged" coupling constant, J_{AB} of *ca.* 7 cps. The very similar value of J_{BC} may again be the result of no conformational preferences, *i.e.*, equal populations of the two *gauche* and *trans* rotamers (Chart I).

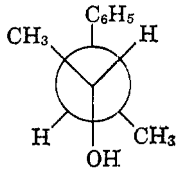
Chart I



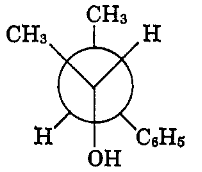
erythro-I (*gauche*)



threo-I (*gauche*)



erythro-I (*trans*)



threo-I (*trans*)

Alternatively, the J_{BC} value of *ca.* 6.7 cps may result from a fortuitous average of *gauche* and *trans* conformers. One possibility is that the population of one *gauche* H–H rotamer (shown in Chart I) may be a factor of 2 larger than the *trans* rotamer (the population of the second *gauche* rotamer being negligible). In either case, the *gauche* rotamer populations are surprisingly large compared to the *trans* populations.[5] Extrapolation to infinite dilution caused a slight increase in J_{BC} to *ca.* 6.9 cps. The hydroxyl resonance absorption moved from 3.71 (2.0 *M* substrate) to *ca.* 0.96 ppm (at minimum observable concentration). The chemical shifts of the other groups in I were relatively constant with increasing dilution. Thus moving from an intermolecular hydrogen-bonded species to monomer has little effect on the rotamer populations. Intramolecular hydrogen bonding to phenyl is a strong possibility,[18] but the trend of the data seems to favor intermolecular hydrogen bonding, particularly at high concentration (2 *M*). The aromatic resonance absorption was a broad singlet at all concentrations, possibly owing to the rapid rotation about the C-phenyl bond.

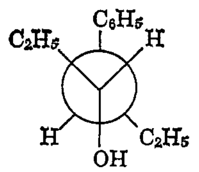
The data for *threo*-I is rather similar to *erythro*-I. The multiplicity of absorptions is the same and chemical shift data are similar. The vicinal coupling constant is slightly smaller than for the *erythro* case, 6.3 *vs.* 6.7 cps. The *gauche* H–H rotamers again are dominant, but substantial populations of the *trans* rotamer are present.

The greater steric hindrance in *erythro*-II (R_A = methyl, R_D = ethyl) has very little effect on the vicinal coupling constant. Proton B appears as a quintet, and the coupling constant is *ca.* 6.7 cps, very similar to *erythro*-I. The two *gauche* populations again slightly outweigh the *trans* rotamer populations.

Proton C does appear to be more complex than previously, possibly owing to the greater steric hindrance at that asymmetric center. The pattern for C appears to be a double triplet, rather than a quartet (Figure 1). However, overlapping resonance absorptions cast some doubt on this conclusion.

threo-II is somewhat similar to *erythro*-II. Again the vicinal coupling constant is somewhat smaller for the *threo* isomer than for the *erythro* (6.0 *vs.* 6.7 cps).

For *erythro*-III (R_A, R_D = ethyl), proton B as well as proton C appears as a double triplet. Two coupling constants can be determined for B, 7.3 and 3.2 cps. The larger value appears to be repeated for proton C. Irradiation at the frequency of the methylene group of R_A (*ca.* 75 cps) collapses the B pattern to a doublet, eliminating the 3.2-cps coupling constant. The value for J_{BC} then is 7.3 cps. This value is somewhat larger than the 6.7-cps value observed for *erythro*-II, showing



erythro-III (*trans*)

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[18] I. Goldman and R. Crisler, *J. Org. Chem.*, **23**, 790 (1958). For infrared data on these compounds, see ref 5. In particular, *threo*-I showed intense infrared absorptions at 3495 and 3620 cm^{-1} (1.9% in CCl_4). Approaching infinite dilution, the 3495-cm^{-1} peak disappeared entirely. Intramolecular hydrogen bonding was apparent as a shoulder to the 3620 cm^{-1} peak. See J. Sicher, M. Cherest, Y. Gault, and H. Felkin, *Collection Czech. Chem. Commun.*, **28**, 72 (1963).

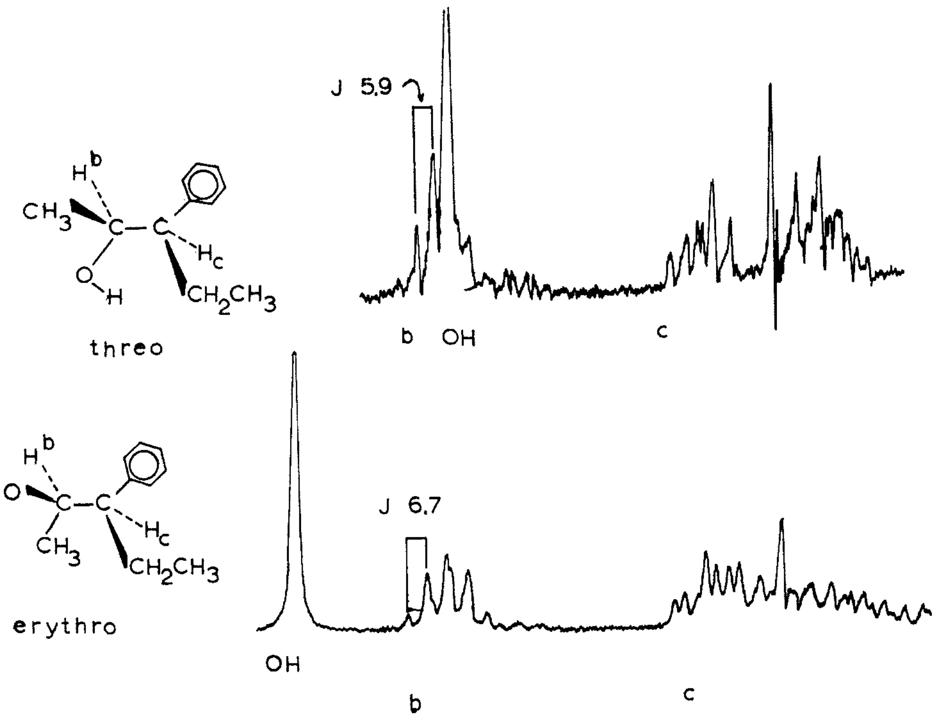


Figure 1.—The assumed predominant conformations in *erythro*- and *threo*-3-phenyl-2-pentanol (II) and the partial nmr spectra.

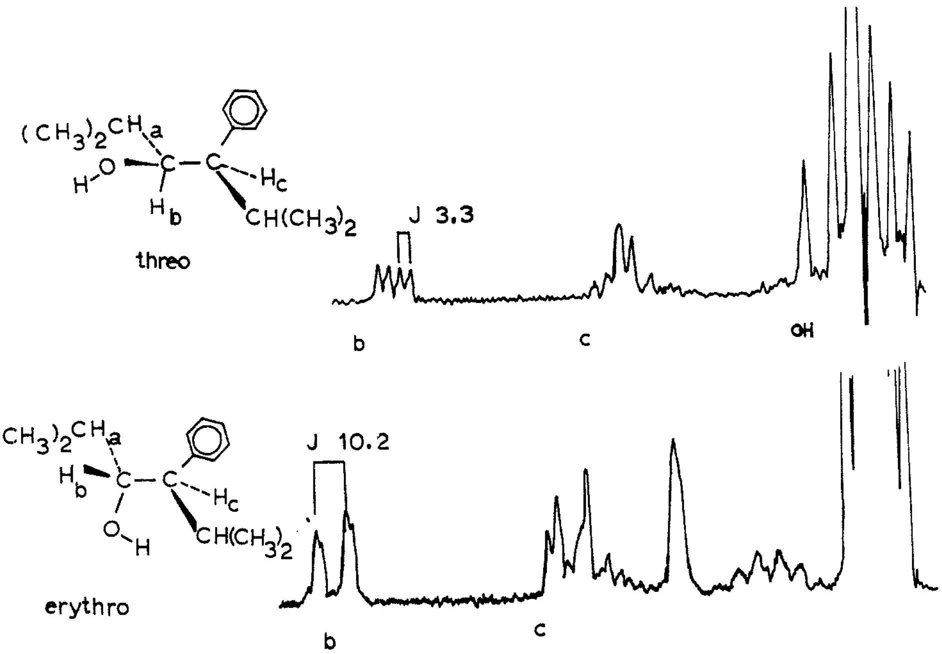


Figure 2.—The assumed predominant conformations in *erythro*- and *threo*-2,5-dimethyl-4-phenyl-3-hexanol (IV) and partial nmr spectra.

that increased steric hindrance increases the population of the *trans* rotamer. For the first time the phenyl resonance absorption is complex, indicating nonequivalent protons in the phenyl group, perhaps owing to hindered rotation, or, on the other hand, possibly this is related to the increased population of the *trans* rotamer.

The most interesting spectra result for compound IV (R_A, R_D = isopropyl) for which models show severe steric hindrance (see Figure 2). For the *erythro* isomer, proton B appears as a double doublet; the two coupling constants are 10.3 and 1.6 cps. Spin-decoupling experiments show that the larger value is J_{BC}. Irradiation at the methine frequency of R_A (*ca.* 84 cps) collapses the double doublet into a doublet, $J = 10.3$ cps. This value is repeated in the proton C pattern. This near-maximum coupling constant indicates that the *trans* rotamer now greatly predominates over the *gauche*.

Assuming that the maximum coupling constant (pure *trans*) is 12 cps while pure *gauche* is 2 cps, and assuming that the observed value results from mixing x parts of *trans* with $(1 - x)$ parts of *gauche*, an equilibrium constant and free energy may be calculated.[13]

$$12x + (1 - x)2 = 10.3$$
$$x = 0.83$$
$$K_{gauche\text{-}trans} = \frac{0.83}{0.17} = 4.9$$
$$\Delta F = -RT \ln K = -970 \text{ cal}$$

This may be compared to the value derived for *erythro*-I, *ca.* +70 cal, some 1040-cal difference favoring the *trans* rotamer in IV. These energy values, of course, are greatly dependent upon the J values assumed for pure *trans* and pure *gauche* conformations.

Some variable-temperature experiments are also listed in Table I. At 100° the vicinal coupling constant assumes a slightly lower value, 9.5 cps, showing that the *gauche* rotamers become somewhat more important at the higher temperature. Increasing the temperature simplifies the complex phenyl absorption a great deal.

For this isomer, the methyl groups of the isopropyls are magnetically nonequivalent, each of the four appearing as a doublet (from coupling to a methine proton).

threo-IV shows the opposite trend from the *erythro* isomer. Protons B (and also C) again appear as double doublets, with coupling constants of 3.6 and 7.6 cps discernible. Spin-decoupling experiments in this case prove that $J_{BC} = 3.6$ cps, showing that one of the *gauche* rotamers is dominant.

The aromatic group in *threo*-IV is a singlet, compared to the complex resonance absorption observed in the *erythro* isomer. This single resonance absorption was not changed upon cooling to −50°. Although the aromatic group would seem to occupy a more sterically hindered position in the *threo* isomer, the aromatic protons approach magnetic equivalence, possibly owing to a fortuitous combination of magnetic parameters, or possibly owing to rapid rotation of the phenyl group.

Comparison of 3-phenyl-2-butanol (I) and 3-cyclohexyl-2-butanol (V) demonstrates the greater steric hindrance due to the cyclohexyl group than due to a phenyl group. Proton B of I is a quintet while proton B of *erythro*-V is a double quartet. The coupling constants cannot be unequivocally assigned, but J_{AB} is taken as 6.4 cps, similar to I, while J_{BC} is tentatively assigned as 4.0 cps. The *gauche* rotamers in this case appear to be the dominant conformers.

threo-V was rather similar to *threo*-I; proton B is a quintet, $J_{BC} = J_{AB} = 6.5$ cps. It is interesting to note the difference in multiplicity; proton B appears as a double quartet in the *erythro* isomer and a quintet in *threo* case (Figure 3).

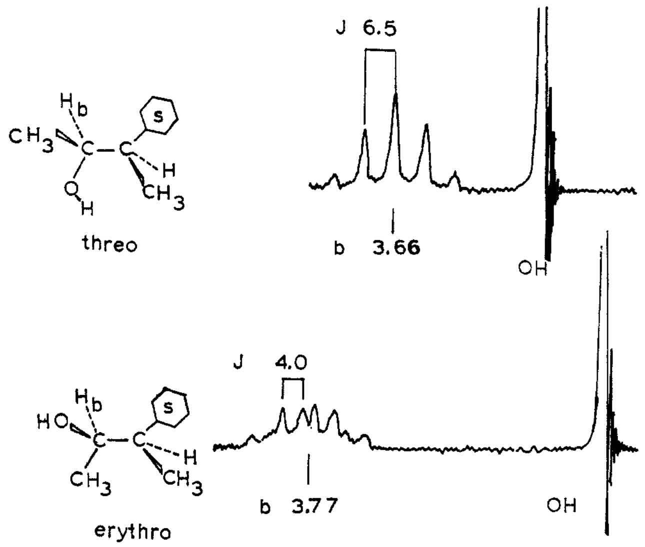
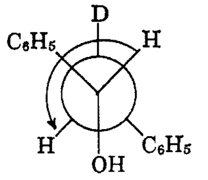


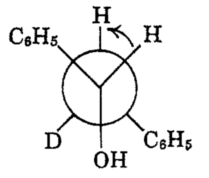
Figure 3.—The assumed predominant conformations in *erythro*- and *threo*-3-cyclohexyl-2-butanol (V) and the partial nmr spectra.

Compound VI is interesting because the *erythro* and *threo* forms must necessarily have the same conformation in which deuterium and hydrogen occupy alternant positions in the two isomers. The coupling constant for *erythro*-VI is 8.4 cps, while the value for *threo* is 4.9 cps. The *erythro* value is lower than expected, showing substantial incursion of the *gauche* H–H conformation.

The average dihedral angle between the vicinal protons may be calculated from the Karplus relationship.[19] For the *erythro* isomer the value is 163°, whereas for the *threo* isomer the value is 39°. As the Newman projections show, the difference between the *erythro* value and the *threo* value should reflect the value for the dihedral angle between geminal hydrogen and deuterium. The theoretical dihedral angle between sp^3-hybridized groups, of course, is 120°; the observed value is 124°, in this case.



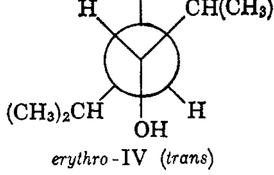
erythro-VI



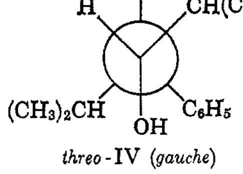
threo-VI

It is rather interesting to note the effect of steric hindrance on conformation. When groups R_A and R_D are rather small, *e.g.*, methyl, no strong conformational preferences are evident, either in the *erythro* or *threo* diastereomers. That is, both the *gauche* and *trans* H–H conformations make substantial contributions to the equilibrium mixture. The "averaged" coupling constant, *ca.* 5–7 cps, is frequently observed, which in other compounds is taken as indicative of no conformational preferences.

As the size of the R groups is increased, the *erythro J* values increase to near the maximum value. On the other hand the *threo J* values diminish to near the minimum value.[20] In either case, when R is isopropyl, these groups strongly prefer a *trans* orientation, as the Newman projections show.



erythro-IV (*trans*)



threo-IV (*gauche*)

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[19] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

[20] This is not a general rule, since in other sets of diastereomers both *erythro* and *threo* isomers tend toward high J values with increasing steric hindrance.

With one exception, the *erythro J* value was larger than the *threo* value. This appears to be a rather general phenomenon.[21]

In general, the large groups in the *erythro* series appear to prefer a *trans* orientation, *e.g.*, cyclohexyl–methyl in V, and isopropyl–isopropyl in IV. In the *threo* series of compounds, the situation is complex and each case must be considered individually.

Experimental Section

The synthesis and properties of I–V have been described in earlier work.[22–25] Compound VI was prepared by the method of Curtin and Kellom[26]: mp 63–64° for each isomer.

Acknowledgments.—Compounds I–V were the generous gift of Dr. D. J. Cram. This work was supported in part by the National Science Foundation Grant GP-3551.

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[21] C. A. Kingsbury, unpublished results.

[22] D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2129 (1952).

[23] D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 3189 (1953).

[24] D. J. Cram, H. L. Nyquist, and F. A. Abd Elhafez, *ibid.*, **79**, 2870 (1957); D. J. Cram and J. Knight, *ibid.*, **76**, 5335 (1954).

[25] D. J. Cram and J. Tadanier, *ibid.*, **81**, 2737 (1959).

[26] D. Y. Curtin and D. B. Kellom, *ibid.*, **75**, 6011 (1953).

The Synthesis and Reactions of 1-Carbamyl-11-ketoindeno[1,2-*c*]isoquinoline[1]

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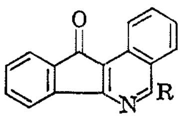
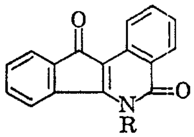
Received June 28, 1965

The reaction of phthalaldehyde with sodium cyanide formed 1-carbamyl-11-ketoindeno[1,2-*c*]isoquinoline (Ia). Evidence for this structure was the infrared spectrum, its reactions, and synthesis of several reaction products. The amide Ia was hydrolyzed to 1-carboxy-11-ketoindeno[1,2-*c*]isoquinoline (Ib) which was converted with zinc and acetic acid to the known 11H-indeno[1,2-*c*]isoquinoline. Oxidation with copper sulfate in pyridine gave 11-ketoindeno[1,2-*c*]isocarbostyril (IIa), which was synthesized by the ammonolysis of 11-ketoindeno[1,2-*c*]isocoumarin.

The reaction of phthalaldehyde with sodium cyanide was studied as a possible method for the preparation of a dibenzocyclooctane derivative. The compound actually isolated was 1-carbamyl-11-ketoindeno[1,2-*c*]isoquinoline (Ia).



Ia, $R=CONH_2$
b, $R=COOH$
c, $R=COOC_2H_5$
d, $R=H$
e, $R=CN$
f, $R=OC_2H_5$
g, $R=Cl$



IIa, $R=H$
b, $R=CH_3$

Evidence for this structure was obtained from its reactions and infrared spectrum. The latter gave absorption (in μ) at 2.95 and 3.12 for the amide hydrogens, 5.85 for the ketone group, 6.03 for the amide carbonyl, and 6.16, 6.25, 6.36, 6.42, and 6.6 for the aromatic region. Complex absorptions in the aromatic region of this type are also shown by isoquinolines.

The presence of the amide grouping was confirmed chemically by hydrolysis with sulfuric acid to acid Ib and ethanolysis by hydrogen chloride in ethanol to ester Ic. The use of hydrochloric acid alone caused hydrolysis and decarboxylation to 11-ketoindeno-[1,2-*c*]isoquinoline (Id) which formed an oxime. No drastic changes occurred in the formation of acid Ib since it was reconverted to the amide by treating the acid chloride, formed with thionyl chloride, with ammonia.

Amide Ia behaved normally with dehydrating agents and was converted to the nitrile Ie by either phosphorus pentoxide or a mixture of benzoyl chloride in pyridine. This compound (Ie) showed a weak absorption maximum at 4.45 μ for the cyano group in its infrared spectrum and, when treated with sodium ethoxide, underwent a nucleophilic substitution similar to that observed for 1-substituted isoquinolines[2,3] and gave the ethoxy compound If.

The ethoxy compound If was easily cleaved with alkali to the isocarbostyril IIa which could also be prepared by the action of alkali on the cyano derivative Ie and the oxidation of the amide Ia in pyridine by copper sulfate. Rearrangements in these reactions were precluded by the synthesis of the nitrile Ie from the isocarbostyril IIa; treatment of the latter with phosphorus oxychloride gave the chloro compound Ig which, upon heating with cuprous cyanide, gave the nitrile Ie.

The isocarbostyril IIa was soluble in alcoholic alkali and converted in this medium by dimethyl sulfate to the N-methylisocarbostyril IIb. The latter was cleaved by alcoholic alkali to 2-(carboxyphenyl)-1,3-indandione which, upon treatment with acid, gave 11-ketoindeno[1,2-c]isocoumarin.[4] The isolation of the latter suggested that an isocarbostyril ring system was involved in the compounds reported. The isocarbostyril structure (IIa) was confirmed by its synthesis from the isocoumarin and ammonia and by the reductive decarboxylation of the acid Ib with zinc and acetic acid to the known 11H-indeno[1,2-*c*]isoquinoline.[5]

Further reactions of the isocarbostyril IIa were in agreement with its structure. Reduction by zinc and alkali gave the 11-hydroxy compound III, and oxida-

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[1] Abstracted in part from the Ph.D. theses of J. K. Stowell, June 1965, and R. E. Karll, June 1949.

[2] S. Gabriel, *Ber.*, **19**, 830, 2354 (1886).

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