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Color Reaction Product of Urea with Diacetyl Monoxime and Glucuronolactone. III.[1] Structures of Two Major Reaction Products of the Color Reaction of Butylurea with 1-Phenyl-1,2-propanedione

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Two crystalline color reaction products were isolated from the reaction mixture of butylurea with 1-phenyl-1,2-propanedione in dioxane containing HCl. One of them (A) was found to be identical with 1,3′-dibutyl-5,5′-diphenyl-2,2′-dioxo-4,4′-diimidazolylmethane (I) which was isolated previously. The other one (C) was found to be isomeric with compound (B) which was also isolated previously. It was found that the only difference between B and C is the positions of their butyl side chains. In order to decide the positions of the side chains of B and C, the differences between the physico-chemical properties expected to be shown by 3,3′-dibutyl-(II) and by 1,1′-dibutyl-5,5′-diphenyl-2,2′-dioxo-4,4′-diimidazolylmethane (III) were estimated theoretically. From the results of this estimation the structures II and III could be assigned to B and C, respectively.

Keywords——van der Waals' radii; CNDO/2 method; color reaction product; butylurea; 1-phenyl-1,2-propanedione; NMR spectrum; UV spectrum; interatomic distance; steric hindrance; IR spectrum

In the previous paper of this series[1] the isolation of two crystalline reaction products (A[3] and B) from the reaction mixture of butylurea with 1-phenyl-1,2-propanedione and glucuronolactone in aqueous phosphoric acid was reported. A and B were shown to be isomeric, having a common 5,5′-diphenyl-2,2′-dioxo-4,4′-diimidazolylmethane basic structure. With regard to the positions of the two butyl side chains, A was found to have these side chains at the 1,3′ positions (I), but it was not possible to decide whether the side chains of B are located at the 3,3′ (II) or 1,1′ (III) positions.

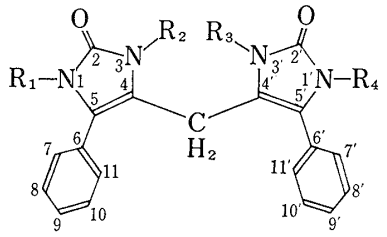
In a later study of this series, it was found that the reaction of butylurea with 1-phenyl-1,2-propanedione in dioxane containing concentrated HCl afforded a new crystalline reaction product (C). C was found to be an isomer of both A and B; namely, its side chains must be located either at the 1, 1′ positions if the side chains of B are located at the 3, 3′ positions or *vice versa*. The isolation of both isomers (B and C) enabled us to observed differences of their physico-chemical properties arising from the difference of side chain positions. It was then possible to decide which of the isomers has its side chains at the 1,1′ positions. This paper describes the results.

Results and Discussion

Isolation of C

Reaction of butylurea with 1-phenyl-1,2-propanedione under the conditions used for the synthesis of tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione derivatives from α-dioxo-com-

1) Part II: K. Kouno and Y. Ueda, *Chem. Pharm. Bull.*, **19**, 110 (1971).
2) Location: *a*) *22-1, Tamagawa-cho, Minami-ku, Fukuoka 815, Japan*; *b*) *Maedashi 3-1-1, Higashi-ku, Fukuoka 812, Japan.*
3) The absorption maximum of A in EtOH was misprinted as 291 nm in the previous paper.[1] It should be 285 nm.



I: $R_1=R_3=C_4H_9$, $R_2=R_4=H$
II: $R_1=R_4=H$, $R_2=R_3=C_4H_9$
III: $R_1=R_4=C_4H_9$, $R_2=R_3=H$

Chart 1

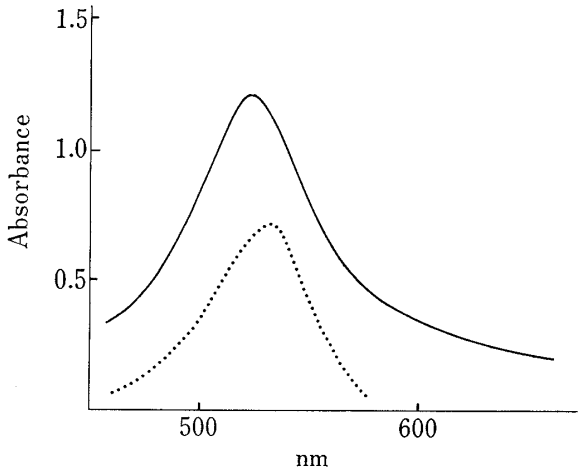


Fig. 1. Absorption Curves of the Color Reaction Mixture and C

——: color reaction mixture, λ_{max} 524 nm.
·····: C, λ_{max} 533 nm.

pounds and urea derivatives[4] afforded two crystalline reaction products, A and a new compound (C). The results of elemental analysis and mass spectral determination of the molecular weight indicated that C has the same molecular formula, $C_{27}H_{32}N_4O_2$, as A and B. The spot of C on a thin-layer chromatogram (TLC) showed a pink color on exposure to HCl vapor, and it had the same *Rf* value as one of the three major color reaction products of butylurea with 1-phenyl-1,2-propanedione (or its monoximes).[1] Therefore C must be the compound which we failed to isolate in the previous study.

C developed a red color immediately after dissolution in the color reaction medium (a mixture of 5% aqueous acetic acid, 85% phosphoric acid and water in a ratio of 1: 3: 3). It was found that the color intensified gradually on standing at room temperature without any shift of its absorption maximum. The closeness of its absorption maximum (533 nm) to that of the color reaction mixture (524 nm) (Fig. 1) suggests that C is the most important color reaction product, because absorption maxima of A and B in the same medium are known to be at 560 nm and 607 nm, respectively.[1]

Nuclear magnetic resonance (NMR), infrared absorption (IR) and ultraviolet absorption (UV) spectra of C (shown in Table I) and its molecular formula indicate that this compound has two phenyl rings, two imidazolone rings, two butyl groups and a $=\dot{C}-CH_2-\dot{C}=$ group. The NMR spectrum showed that two protons of two NH groups are magnetically equivalent and six protons of two terminal methyl groups of two butyl side chains are also magnetically equivalent. Therefore, the chemical structure of C is considered to be either 3,3′-dibutyl-5,5′-diphenyl-2,2′-dioxo-4,4′-diimidazolylmethane (II) or 1,1′-dibutyl-5,5′-diphenyl-2,2′-dioxo-4,4′-diimidazolylmethane (III). Namely C is an isomer of both A and B.

The Assignment of the Chemical Structure II to B and That of III to C

When we compare the UV, NMR and IR spectra of B with those of C, the following clear differences are seen: the chemical shift assigned to the two protons of the $=\dot{C}-CH_2-\dot{C}=$ group in the NMR spectrum, the wavelength of the absorption maximum in the UV spectrum and some absorption bands (ν_{N-H} and $\nu_{C=O}$) in the IR spectrum.

The two protons of the $=\dot{C}-CH_2-\dot{C}=$ group (this group will be called hereafter the central CH_2 group) were detected as a singlet in the NMR spectra of both B and C. The chemical shifts of these protons of B and of C were found to be 4.41 and 3.97 ppm (δ), respectively.

4) H. Biltz, *Ber.*, **40**, 4811 (1907).

Table I. Spectral Data for B and C

	B	C	
UV λ_{max}^{EtOH} (nm, ε)	291 (21700)	275 (10200)	
IR ν_{max}^{KBr} (cm^{-1})	1670, 1680, 3150	1670, 1693, 3180	
NMR (δ, ppm)[a]	(in CF_3COOH)	(in CF_3COOH)	(in C_5H_5N)
C–C–CH_3	0.92 (6H, m)	0.82 (6H, m)	0.65 (6H, m)
C–$(CH_2)_2$–C	*ca.* 1.0—1.7 (8H, m)	*ca.* 1.0—1.8 (8H, m)	*ca.* 0.95—1.8 (8H, m)
N–CH_2–C	3.73 (4H, m)	3.76 (4H, m)	3.70 (4H, m)
=C–CH_2–C=	4.41 (2H, s)	3.97 (2H, s)	3.73 (2H, s)
Arom.H	7.51 (10H, m)	7.24 (4H, m) 7.54 (6H, m)	
NH	11.05 (2H, b)	10.79 (2H, b)	11.55 (2H, b)

a) The following abbreviations are used: s, singlet; m, multiplet; b, broad. Chemical shifts of B determined in C_5H_5N are taken from the previous paper.[1]

The magnetic equivalency of the two protons of the central CH_2 group means primarily that the spatial relationship between one of these two protons and the two phenyl rings must be the same as that between the other proton and the two phenyl rings in both B and C, because phenyl rings located in the neighborhood of these protons would exert powerful anisotropic effects on these protons, so if the spatial relationships were different, a singlet signal would not be expected. It was also considered that the spatial relationship between one of the above two protons and the planes of the two double bonds of the imidazolone moieties of the molecule should be the same as that between the other proton and these two planes. The difference between the chemical shifts of protons of the central CH_2 groups of B and C was thought to be attributable mainly to the difference of the spatial relationship between the two protons of the central CH_2 group and the two phenyl rings in B and C, because the anisotropic effect of double bonds on these protons is considered to be less than that of phenyl rings. Hereafter the spatial relationship between the protons of the central CH_2 group and the two phenyl rings will be called simply the spatial relationship.

In order to assign the structures of B and C, it was thought that theoretical estimation of the differences of physico-chemical properties expected to exist between II and III would be useful. As mentioned before, both B and C can be considered to have symmetric structures with respect to the protons of their central CH_2 groups, so the basic 5,5′-diphenyl-2,2′-dioxo-4,4′-diimidazolylmethane structure of II and III must have a two-fold axis of symmetry. A plane of symmetry cannot become a symmetry element, because it dose not require equality of the spatial relationship between one of the protons of the central CH_2 group and the two phenyl rings with that between the other proton of the same group and the two phenyl rings.

The difference between the spatial relationship of B and that of C must arise from the difference between the positions of the two side chains of B and those of C. In other words, the magnitude of steric hindrance of the two butyl groups of B to both of two kinds of rotations (rotations of the phenyl rings and rotations of the two imidazolone rings) must be different from that of C. Thus, it is necessary to estimate the magnitude of the steric hindrance theoretically in both cases. In this theoretical estimation, if we treat the entire structures of II and III the calculations would become considerably complex, because each butyl group has three C–C bonds and all of them are also capable of free rotaction. Incidentally, the steric hindrance of a butyl group to the above-mentioned rotations is considered to arise mainly from the CH_2 group adjacent to the N atom. Therefore, methyl groups were substituted for butyl groups in both II and III in this theoretical estimation. Hereafter these modified structures of II and III will be designated as II-CH_3 and III-CH_3, respectively.

The method of theoretical estimation of the magnitudes of steric hindrances in II-CH_3 and III-CH_3 was as follows. The two phenyl rings were rotated to the same degree, one ring about the $C_{(5)}$–$C_{(6)}$ bond counterclockwise with respect to the $C_{(5)}$ atom and the other ring about the $C_{(5')}$–$C_{(6')}$ bond counterclockwise with respect to the $C_{(5')}$ atom. At each of the above rotation angles the two imidazolone rings were rotated to the same degree, both counterclockwise with respect to the C atom of the central CH_2 group, one ring about the bond connecting $C_{(4)}$ with the C atom of the central CH_2 group and the other ring about the bond connecting $C_{(4')}$ with the C atom of the same CH_2 group. The former and the latter rotation angles are designated hereafter by θ and ϕ, respectively. Both θ and ϕ were defined as 0° when the two phenyl rings, four C atoms of the two double bonds of the two imidazolone rings and the C atom of the central CH_2 group are all located on the same plane. At each combination of θ and ϕ the interatomic distances of all pairs of two atoms which are not bonded were calculated by a geometrical method. In this calculation all four N atoms of II-CH_3 and III-CH_3 were considered to be capable of rapid interconversion. Next, at each combination of θ and ϕ all of the interatomic distances calculated were compared with the sum of the van der Waals' radii[5] of the corresponding two atoms. The results showed that two methyl groups cannot be located at the 3,3′ position, whatever the values of θ and ϕ, if we assume that steric hindrance exists between two atoms having a smaller interatomic distance than the sum of the van der Waals' radii. This result is not consistent with the presence of two isomeric compounds, B and C. Therefore, it was necessary to know to what extent two atoms can approach each other without suffering steric hindrance. X-ray crystallographic data for several compounds[6] indicated that two atoms can approach to within an interatomic distance of about 75% of the sum of their van der Waals' radii (Table II). Therefore, it was supposed that combinations of θ and ϕ at which at least one of the interatomic distances calculated is shorter than 75% of the sum of the van der Waals' radii of the corresponding two atoms can be excluded. On this basis, the ranges of possible variation of θ and ϕ for II-CH_3 and III-CH_3 were decided to be θ (110—160°)—ϕ(70—90°) and θ(80—100°)—ϕ(50—120°), respectively. If $\theta' = -\theta$ and $\phi' = -\phi$, two conformations, one defined by a combination of θ and ϕ and the other defined by a combination of θ' and ϕ', are in a mirror image relation. This means that

Table II. The Ratio of Interatomic Distance to the Sum of van der Waals' Radii

Compound	Pair of atoms	Interatomic distance (Å)	Sum of van der Waals' radii (Å)	Ratio of interatomic distance to sum of van der Waals' radii (%)
2,2′-Dibromo-biphenyl	($Br_{(2)}$—$Br_{(2')}$)	3.61	3.90	92.6
2,2′-Dimethyl-4,4′-diamino-biphenyl	($C_{(Me)}$—$C_{(Me)}$)	3.58	4.00	89.5
Nitro-mesitylene	($C_{(Me)}$—$O_{(NO_2)}$)	2.99	3.40	87.9
3,3′-Dibromo-benzophenone	($C_{(2)}$—$C_{(2')}$)	3.06	3.70	82.7
1-Phenyl-2,3-dimethyl-4-bromo-5-pyrazolone	($C_{(ph-2')}$—$C_{(Me)}$)	2.88	3.85	82.7
	($C_{(ph-6')}$—O)	3.01	3.25	92.6
Bis(4-methoxyphenyl)aminyl oxide	($C_{(2)}$—$C_{(2')}$)	3.09	3.70	83.5

5) J.A. Dean (ed.), "Lange's Handbook of Chemistry," 11th ed., McGraw-Hill, New York, 1973, Section 3, p. 118; L. Pauling, "The Nature of the Chemical Bond and the Structure of Molecules and Crystals," 3rd ed., Cornell University Press, Ithaca and New York, 1960.

6) L.E. Sutton (ed.), "Tables of Interatomic Distances and Configuration in Molecules and Ions," The Chemical Society, London, 1958 and 1965.

the spatial relationship of one conformation is the same as that of the other conformation. Therefore, only absolute values of both θ and ϕ are shown in the ranges mentioned above, as will be discussed later.

Total energies of all structures of II-CH_3 and III-CH_3 having conformations defined by the possible combinations of θ and ϕ in the ranges mentioned above were calculated by the CNDO/2 method.[7] In these molecular orbital calculations all CH_3 groups were supposed to be able to rotate freely about the C–N bond. The results showed that the most stable conformations of II-CH_3 and III-CH_3 are those defined by $\theta(120°)-\phi(80°)$ and $\theta(80°)-\phi(110°)$, respectively. Since it is thought that the energy barrier to the internal rotation of the C–C bond of ethane is about 3 kcal/mol (0.13 eV), it was supposed that any conformation whose calculated total energy is more than 0.13 eV higher than that of the most stable conformation mentioned above must be unstable. On this basis, the ranges of possible variation in the combinations of θ and ϕ for II-CH_3 and III-CH_3 were further narrowed to $\theta(120—135°)-\phi(70—80°)$ and $\theta(80—100°)-\phi(90—110°)$ (excluding the combination of $\theta(80°)-\phi(90°)$), respectively. Since a butyl group is much wider than a methyl group, the corresponding ranges of structures of II and III having butyl side chains are considered to be much narrower than those shown above.

Finally, differences between the physico-chemical properties expected to be shown by II-CH_3 and III-CH_3, in which the combinations of θ can vary only in the ranges mentioned above, were estimated theoretically. The difference between chemical shifts of protons of their central CH_2 groups were estimated by Bovey's method.[8] The results showed that the deshielding effects (ppm) of II-CH_3 and III-CH_3 are in the ranges of $+0.40$——-0.06 and -0.21——-0.48, respectively. Here, a positive value means greater deshielding and a negative value means smaller deshielding. Thus, the proton signal of the central CH_2 group of II is expected to be deshielded relative to that of the corresponding protons of III.

The protons of the central CH_2 group of B were found to be deshielde relative to the corresponding protons of C by 0.44 ppm (Table I). Therefore, the structures II and III can be assigned to compounds B and C, respectively.

The ranges of possible variations of θ mentioned above indicated that the imidazolone ring of III-CH_3 is much more orthogonal to the plane of the phenyl ring than in the case of II-CH_3. This means that the degree of π electronic conjugation between the imidazolone ring and the phenyl ring must be larger in II than in III. Thus, the ultraviolet absorption maximum of II is expected to be located at longer wavelength than that of III. B and C were found to show absorption maxima at 291 and 275 nm, respectively. These experimental results support the assignments made above on the basis of theoretical calculations.

Experimental

All melting points are uncorrected. UV spectra were recorded on an MPS-50L spectrometer, IR spectra were recorded on a DS-301 spectrometer, MS spectra were recorded on a JMS-OISG spectrometer and NMR spectra were recorded on a JNM C-60-H spectrometer at 60 MHz using TMS as an internal standard. TLC was carried out by the procedure described in the preceding paper.[1]

Isolation of C——An MeOH solution (*ca.* 150 ml) of 3.7 g (0.025 mol) of 1-phenyl-1,2-propanedione and 5.8 g (0.05 mol) of butylurea was treated with 1.5 ml of conc.HCl. The solution was refluxed in a boiling water bath for 2.5 hr, and left to stand at room temperature overnight. The solvent was removed by distillation *in vacuo*, and the residue was dissolved in BuOH. BuOH solution was washed successively with H_2O, sat. aq. $NaHCO_3$, and H_2O, then dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was dissolved in MeOH–AcOEt (1: 99) and subjected to chromatographic separation on Al_2O_3. The crystalline residue left on evaporation of a few early fractions was crystallized from acetone–MeOH. Repeated

7) J.A. Pople and D.L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, 1970.

8) F.A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, Inc., New York and London, 1969; C.E. Johnson, Jr. and F.A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

recrystallization from the same solvent mixture gave *ca.* 40 mg of pure faint yellow needles of mp 238—239° (dec.). IR spectra, melting point and *Rf* value on TLC coincided with those of A previously obtained. No depression was observed on mixed melting point determination with A.

The next few fractions eluted by a mixture of MeOH and acetone (1: 1) afforded another crystalline residue. Repeated recrystallization from acetone–MeOH afforded *ca.* 40 mg of pure faint yellow prisms (C) of mp 246—249° (dec.). *Anal.* Calcd for $C_{27}H_{32}N_4O_2$: C, 72.95; H, 7.26; N, 12.60. Found: C, 72.91; H, 7.05; N, 12.95. MS *m/e* 444 (M^+).

Compound C is soluble in $CHCl_3$, CH_2Cl_2, MeOH and EtOH, slightly soluble in acetone and benzene and sparingly soluble in H_2O, ether and AcOEt.

Values for all atomic distances and bond angles of phenyl rings, CH_3 groups and the central CH_2 groups of II-CH_3 and III-CH_3 were taken from the literature.[7] Values for bond angles of the remaining moieties were assumed to be as follows: bond angles of an imidazolone ring, ∠N–C–C=107°, ∠C–N–C=108°, ∠N–C–N=110°; bond angles between an imidazolone ring and a phenyl ring, ∠N–C–C=∠C–C–C=126.5°, bond angles between an imidazolone ring and the C atom of the central CH_2 group, ∠N–C–C=∠C–C–C=126.5°; bond angles of a N–CH_3 and a N–H groups, ∠C–N–CH_3=∠C–N–H=109.84°, ∠H–N–lone pair electrons=∠H_3C–N–lone pair electrons=109.47°. The values for imidazolone rings were the mean values of the corresponding angles of imidazole[9] and parabanic acid.[6]

All calculations were carried out on FACOM 230-75 and FACOM M-190 computers at the Computation Center of Kyushu University.

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9) G. Will, *Z. Kristallogr.*, **129**, 221 (1969).