[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

THE REPLACEABILITY OF CERTAIN METHYLENE GROUPS AND THE RELATION OF CONSTITUTION TO THE STABILITY OF A C=C LINKAGE

H. V. MOYER[1] AND F. B. DAINS

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In a previous series of papers,[2] it has been shown that the methylene hydrogen in many compounds when heated with the substituted formamidines could be readily replaced by the anilidomethylene grouping, thus synthesizing a C=C bonding.

$$>CH_2 + RN{=}CHNHR = >C{=}CHNHR + RNH_2$$

An exception was noted in the case of methylisoxazolone, which gave only tarry products with diphenylformamidine. Further experiments showed, however, that the benzal derivative reacted easily and smoothly with the formamidine, yielding the anilidomethylenemethylisoxazolone, as follows:

$$CO{-}O{-}N{=}C(CH_3)C{=}CHC_6H_5 + C_6H_5N{=}CHNHC_6H_5 =$$
$$CO{-}O{-}N{=}C(CH_3)C{=}CHNHC_6H_5 + C_6H_5CH{=}NC_6H_5$$

The reaction was unusual since it involved the separation of carbon from carbon and the formation of another C=C linking. It seemed worth while to investigate this further and the following paper is a preliminary study of the types of compounds which lend themselves to such an interchange.

$$R_2C{=}CHC_6H_5 + R'N{=}CHNHR' = R_2C{=}CHNHR + R'N{=}CHR'$$

Thus far the replacement has been successful only in the case of the aldehyde (RCH=) derivatives of certain heterocyclic rings, namely: isoxazolone, pyrazolone and rhodanine (thiazolidone) and is probably confined to those compounds in which the benzal group can be removed easily by hydrolysis with dilute acids or heating with phenylhydrazine.

$$R_2C{=}CHR' + HOH = R_2CH_2 + RCHO$$
$$R_2C{=}CHR' + C_6H_5NHNH_2 = R_2CH_2 + C_6H_5NHN{=}CHR'$$

With open chain derivatives such as benzalphenyl cyanide or nitrobenzalacetylacetone it was found impossible to break the double bonding and introduce an aminomethylene grouping.

[1] From a dissertation presented by H. V. Moyer to the Faculty of the Graduate School of the University of Kansas in partial fulfilment of the requirement for the degree of Doctor of Philosophy.

[2] (a) Dains, *Ber.*, **35**, 2509 (1902); (b) Dains and Griffin, THIS JOURNAL, **35**, 962 (1913); (c) Dains and Brown, *ibid.*, **31**, 1148 (1909); (d) Dains and Stephenson, *ibid.*, **38**, 1841 (1916); (e) Dains and Harger, *ibid.*, **40**, 562 (1918); (f) Dains, Thompson and Asendorf, *ibid.*, **44**, 2310 (1922).

Experimental

The Aldehyde Derivatives of 3-Phenylisoxazolone and Diphenyl Formamidine

4-Benzal-3-phenylisoxazolone was readily formed when molar quantities of benzaldehyde and the isoxazolone were heated for a few minutes at the melting point of the mixture. The benzal derivative (5 g.) and diphenylformamidine (4 g.) were heated at 145° until the mixture melted and then at 120° for forty-five minutes. From the reaction product was isolated 2.5 g. of the 4-anilidomethylene-3-phenylisoxazolone,[2b] which was identified by a mixed melting point and analysis.

Anal. Calcd. for $C_{16}H_{12}O_2N_2$: N, 10.61. Found: N, 10.88.

In order to ascertain the effect of other aromatic aldehyde groupings, the piperonal-, anisal-, *m*-nitrobenzal- and cinnamylidenephenylisoxazolones were heated with diphenylformamidine under similar conditions. In all cases the aldehyde grouping was replaced by the anilidomethylene radical. It should be noted that this is the only instance in which the unsaturated cinnamylidene group has been replaced. Later experiments with the cinnamic aldehyde[3] condensation products of other ring compounds gave only tarry products. Negative results were obtained with the furfuralphenylisoxazolone.

Diphenylformamidine with the Aldehyde Derivatives of Various Pyrazolones

The experimental work has shown that the methylene hydrogen as well as the benzal groups in the substituted pyrazolones can be replaced, though the ease is determined somewhat by the nature of the substituents in the ring. Thus from the benzal and piperonal derivative of 1-phenyl-3-methylpyrazolone, $CONC_6H_5N{=}C(CH_3)C{=}CHR$, at 140°, the 4-anilidomethylenepyrazolone (m. p. 154°)[4] was obtained. The ease with which the aldehyde bonding can be broken was shown by the fact that when the piperonalpyrazolone was heated in alcohol solution with phenylhydrazine, piperonalphenylhydrazone and methylphenylpyrazolone were isolated and identified.

1,3-Diphenylbenzalpyrazolone gave at 160° the anilinomethylene derivative (m. p. 140°) alone. This is of advantage since the diphenylpyrazolone with diphenylformamidine yielded both the 140° compound and *bis*-diphenylpyrazolone (m. p. 247°).[4,5]

Anal. Calcd. for $C_{31}H_{22}O_2N_4$: N, 11.62. Found: N, 11.87.

3-Hydroxy-1-phenyl-4-benzalpyrazolone,[6] $CO{-}N(C_6H_5)N{:}C(OH)C{=}CHC_6H_5$, was prepared by heating benzaldehyde and the pyrazolone at 130° or, better, by simply refluxing the components in alcohol solution for an hour. The dark red needles melted at 275°.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: N, 10.60. Found: N, 10.87.

It was heated with diphenylformamidine first at 210° and then at 180° for thirty minutes. From the reaction product was isolated the 1-phenyl-3-hydroxy-4-anilinomethylenepyrazolone, which separated from boiling acetic acid in yellow needles melting at 272–273°. It was soluble in dilute potassium hydroxide and was precipitated unchanged by acids.

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[3] Giua, *Gazz. chim. ital.*, **55**, 567–576 (1925).

[4] Ref. 2c, p. 1154.

[5] Betti and Mundici, *Gazz. chim. ital.*, [1] **36**, 184 (1906).

[6] Michaelis and Burmeister, *Ber.*, **25**, 1509 (1892).

Anal. Calcd. for $C_{16}H_{13}O_2N_3$: N, 15.05. Found: N, 15.34, 14.85.

Corresponding results were obtained on heating the anisalpyrazolone (m. p. 250°)[7] with the formamidine. As a check the same anilinomethylene compound, m. p. 272–273°, was synthesized from the hydroxyphenylpyrazolone by heating with the formamidine at 160°.

3-Phenyl- and 3-Methyl-4-benzalpyrazolone, $CONHNC(R)C{=}CHC_6H_5$.—These pyrazolones differ from the preceding in having the N in position 1 unsubstituted. Both were unchanged after heating with the diphenylformamidine, a result which would seem to show that the double bond becomes more stable as the positive nature of the ring is increased.

3-Methyl-4-anilinomethylenepyrazolone, $CONHN{=}C(CH_3)C{=}CHNHC_6H_5$.—The 3-methylpyrazolone with a free CH_2 grouping reacted only with difficulty. Finally, heating at 200° with a large excess of the formamidine produced a yellow compound melting at 204° which corresponded to the above.

Anal. Calcd. for $C_{11}H_{11}N_3O$: N, 20.9. Found: N, 21.68.

Benzalthiazolidone Derivatives

3-Phenylrhodanine, which illustrates another type of heterocyclic ring, the thiazole, possesses a reactive methylene grouping. Its benzal derivative, $S{-}CSNC_6H_5COC{=}CHC_6H_5$ (m. p., 192°)[8] reacted in like manner with the formamidine at 200° in a sealed tube, yielding the 5-anilinomethylene compound (m. p. 247°).[9]

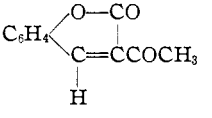
The cinnamylidenephenylrhodanine (m. p. 223°)[10] was unaffected at temperatures below 200°. Above this point, only decomposition products were obtained.

Anal. Calcd. for $C_{18}H_{13}NOS_2$: N, 4.33. Found: N, 4.36.

Benzaldi-*o*-Tolylthiazolidone, $SC(NHC_7H_7)NC_7H_7COC{=}CHC_6H_5$.—The only essential difference between the rhodanine and this compound is in having the S at position 2 replaced by a tolylimino grouping. The change has, however, increased the positive character of the molecule so that the heating at 220° for five hours with the formamidine gave only negative results.

Benzylidene Derivatives in Which the Methylene Carbon Is Not Part of a Ring

To illustrate this type, there were chosen benzalbenzylcyanide, *m*-nitrobenzalacetylacetone and cinnamylidene-acetylacetone. In no case did heating with the formamidine afford any evidence of breaking the C=C linking, although the free methylene compounds reacted readily with the amidine. The same negative result was obtained with acetylcoumarine,



which contains a C=C bonding due to aldehyde condensation with acetoacetic ester.

[7] Asher, *Ber.*, **30**, 1018 (1897).

[8] Andreash and Zipser reported 186°, *Monatsh.*, **24**, 506 (1903).

[9] Dains and Davis, *Kansas Univ. Sci. Bull.*, **15**, 265–270 (1924); *C. A.* **20**, 600 (1926).

[10] Andreash and Zipser found 217°, *Monatsh.*, **24**, 513 (1903).

Benzalacetophenone (Anil Formation with the Ketone Oxygen).—The experiments with benzalacetophenone, while they showed the stability of the double bonding, led to another interesting result. Molar quantities of the ketone and formamidine were heated at temperatures ranging from 130–150°. From the reaction product was isolated in not over 5% yield a compound which crystallized from alcohol in white needles and melted at 168°. Had the reaction involved the substitution of the benzal group, the compound $C_6H_5COCH{=}CHNHC_6H_5$ (m. p. 141°) should have resulted.[11] The 168° product gave the following results on analysis.

Anal. Calcd. for $C_{21}H_{17}N$: C, 89.1, H, 6.00, N, 4.9; mol. wt., 283. Found: C, 88.94, 89.0; H, 6.31, 6.15; N, 4.92, 4.93; mol. wt. 270, 286.

This corresponded, as was proved, to the anil of benzalacetophenone, $C_6H_5CH{=}CHC(NC_6H_5)C_6H_5$. The compound was unsaturated and gave on hydrolysis with dilute sulfuric acid, aniline, acetophenone and benzaldehyde, which indicated that the benzal group had not been removed. The mechanism of the reaction is doubtless the following

$$C_6H_5CH{=}CHCOC_6H_5 + RN{=}CHNHR \longrightarrow C_6H_5CH{=}CHC(NR)C_6H_5 + HCONHR$$

The isolation of *p*-bromoformanilide in one case where di-*p*-bromodiphenylformamidine was used points to this interpretation.

Direct Synthesis of the Phenylimide.—A 10% yield followed when the ketone and freshly distilled aniline were heated at 175° for four hours, but the yield was raised to 80% by using a dehydrating agent.

Thus benzalacetophenone (20 g.), aniline (8.8 g.) and anhydrous sodium acetate (20 g.) were thoroughly mixed and heated at 175° for three hours. The molten mass was poured into a large volume of water and the oily liquid which separated crystallized from alcohol and then from benzene.

As an additional confirmation of this synthesis, *p*-chloro-aniline and *p*-toluidine were used in place of aniline with equal success.

***p*-Chlorophenylimide of Benzalacetophenone,** $C_6H_5CH{=}CHCN(C_6H_4Cl)C_6H_5$, separates from alcohol in white needles which melt at 167°.

Anal. Calcd. for $C_{21}H_{16}ClN$: Cl, 11.16; N, 4.41. Found: Cl, 11.07; N, 4.30.

***p*-Tolyliminobenzalacetophenone** has a melting point of 170°.

Anal. Calcd. for $C_{22}H_{19}N$: N, 4.71. Found: N, 4.78, 4.81.

Action of Bromine on the Phenyl Imino Derivative.—Bromine added to the anil in carbon bisulfide on chloroform solution yielded a precipitate that blackened at 160° and decomposed at 240°.

Analysis showed it to be a mixture, but that addition had mainly taken place on the nitrogen was proved by the fact that one of the hydrolysis products was *p*-bromo-aniline. This is in accord with the fact that in a grouping $C{=}NC_6H_5$, bromine adds to the nitrogen and then rearranges to the *p*-bromo derivative.

Summary

1. An aromatic aldehyde condensed with the methylene hydrogen of an isoxazolone was readily replaced by an anilinomethylene group, yielding a new C=C bonding.

2. The same reaction occurred with the benzalpyrazolones with a phenyl group in the 1-position, but not when this position was unsubstituted.

[11] Claisen and Fischer, *Ber.*, **20**, 2192 (1887).

3. Benzyl cyanide and the benzalacetylacetone were found not to react with the formamidine, though the free CH_2 derivatives did.

4. With benzalacetophenone and the formamidine the anil resulted—a product that was obtained in 80% yield on heating the ketone with aniline and sodium acetate.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

DI-(CYCLOHEXYLALKYL) ACETIC ACIDS. XIV[1]

BY LETHA A. DAVIES[2] AND ROGER ADAMS

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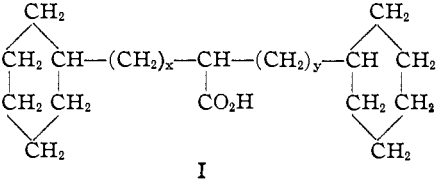
In previous papers it has been demonstrated that when a cyclohexyl group is substituted at the end of a straight-chained aliphatic acid of certain molecular weight, the product is an effective bactericide *in vitro* toward *B. leprae*, whereas the corresponding straight-chained acid with the same number of carbon atoms is ineffective. It has been shown further that if the carboxyl group is removed from the end of the chain to a position nearer to the ring, the effectiveness of the isomeric acid is increased. As a consequence it seemed advisable to prepare a few di-(cyclohexylalkyl) acetic acids for testing, in which the carboxyl group is in the favored position. It is thus possible to determine whether a second ring structure would enhance the bactericidal properties. The compounds prepared are of the general formula represented by I where "x" is 1, 2, 3 or 4 and where "y" is 0, 1, 2 or 3. They were made in the usual way by introducing first one cyclohexylalkyl group into malonic ester and then a second, followed by saponification and heating of the malonic acid.



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The bacteriological results in Table I indicate that no particular ad-

[1] For previous articles in this field see (a) Shriner and Adams, THIS JOURNAL, **47**, 2727 (1925); (b) Noller with Adams, *ibid.*, **48**, 1080 (1926); (c) Hiers with Adams, *ibid.*, **48**, 1089 (1926); (d) *ibid.*, **48**, 2385 (1926); (e) Van Dyke and Adams, *ibid.*, **48**, 2393 (1926); (f) Sacks with Adams, *ibid.*, **48**, 2395 (1926); (g) Noller and Adams, *ibid.*, **48**, 2444 (1926); (h) Adams, Stanley, Ford and Peterson, *ibid.*, **49**, 2934 (1927); (i) Arvin with Adams, *ibid.*, **49**, 2940 (1927); (j) Adams, Stanley and Stearns, *ibid.*, **50**, 1475 (1928); (k) Yohe and Adams, *ibid.*, **50**, 1503 (1928); (l) Arvin and Adams, *ibid.*, **50**, 1983 (1928).

[2] This communication is an abstract of a portion of a thesis submitted by Letha A. Davies in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.