THE JOURNAL OF Organic Chemistry®

Volume 22, Number 6

June 12, 1957

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Flavothebaone. VI.[1] Oxidation of Nitrogen-Free Products

K. W. BENTLEY AND J. P. RINGE

Received December 17, 1956

The oxidation of flavothebaone trimethyl ether hexahydrodesazamethine, dihydrodesaza-ψ-methine, dihydrodesazaneomethine, and of dihydro-Compound-E with chromic acid, results in the production of aromatic ketones, by oxidation of the methylene group adjacent to the veratrole nucleus. In addition the dihydrodesaza-ψ-methine and dihydro-Compound-E have been oxidized by peroxytrifluoroacetic acid, with attack of the ethylenic linkage. All the reaction products have been satisfactorily formulated on the basis of the structures previously assigned to these nitrogen-free products in the flavothebaone series.

In a search for methods of further degradation of flavothebaone derivatives the oxidation of several nitrogen-free products has been investigated. It was hoped thus to open the ketonic ring of the hexahydrodesazamethine (I) and obtain compounds related to the ψ-methine series. Oxidation of the ketone (I) with chromic acid afforded, however, only 10-oxoflavothebaone trimethyl ether hexahydrodesazamethine (II), which gives a dioxime, and shows the infrared absorption bands characteristic of a saturated carbonyl group (1714 cm.$^{-1}$) and an aromatic carbonyl group (1665 cm.$^{-1}$). The same position is attacked by chromic acid in other compounds of the morphine group, *e.g.*, the conversion of morphine into 10-hydroxymorphine.[2] Attempts to oxidize the diketone (II) further failed. The oxidation of flavothebaone trimethyl ether dihydro-desaza-ψ-methine (III, R = CH_3CO) with chromic acid likewise resulted only in converting the methylene group to carbonyl, the product, oxoflavothebaone trimethyl ether dihydrodesaza-ψ-methine, being given the structure of 11-acetyl-12-ethyl-1,2,7,10-tetramethoxy-5-oxo-5,12-dihydrochrysofluorene (IV, R = CH_3CO). This compound, which readily gives a dioxime, contains one saturated and one highly conjugated unsaturated carbonyl group (infrared bands at 1704 and 1640 cm^{-1}) and has an ultraviolet spectrum (λ_{max} 2,600; 2,950, 3,500 Å, ϵ_{max} 11,200; 15,900; 15,900) very similar to that of piperonylidenedihydroflavothebaone trimethyl ether (V)[3] (λ_{max} 2,600; 2,900; 3,500 Å, ϵ_{max} 12,600; 10,000; 14,100), which contains an analogous conjugated system. Further oxidation of the diketone (IV, R = CH_3CO) could not be effected.

Oxidation of ketones to esters using peroxytrifluoroacetic acid has been successfully accomplished by Sager and Duckworth[4] and by Emmons and Lucas,[5] the latter two workers showing that in the oxidation of methyl alkyl ketones the acetate is invariably formed. Accordingly it was hoped that oxidizing the dihydrodesaza-ψ-methine (III, R = CH_3CO) with this reagent might afford a method of removing the CH_3CO group with access to the neomethine series (*vide infra*). Oxidation of the dihydrodesaza-ψ-methine, $C_{25}H_{23}O_5$, in this way, however, afforded only a very small amount of crystalline material, of composition $C_{25}H_{28}O_7$. The ultraviolet spectrum of this product (λ_{max} 3,050 Å, ϵ_{max} 7,770) indicates that the styrenoid double bond is no longer present, and the infrared spectrum (bands at 1733 and 1690 cm.$^{-1}$) indicates the presence in the molecule of an ester group and a carbonyl group, and the structure VI is accordingly suggested for the compound. Insufficient material was obtained for further investigation.

(1) Part V, *J. Org. Chem.*, 22, 424 (1957).

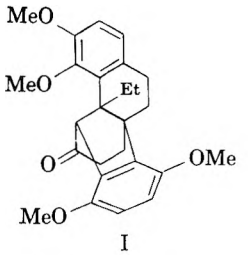
(2) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, 77, 6359 (1955).

(3) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, 22, 418 (1957).

(4) W. F. Sager and A. Duckworth, *J. Am. Chem. Soc.*, 77, 188 (1955).

(5) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, 77, 2287 (1955).

Oxidation of flavothebaone trimethyl ether dihydrodesazaneomethine (III, R = OH) with chromic acid followed the same course as the oxidation of the dihydrodesaza-ψ-methine (III, R = CH_3CO), the product, oxoflavothebaone trimethyl ether dihydrodesazaneomethine, being given the structure of 12-ethyl-11-hydroxy-1,2,7,10-tetramethoxy-5-oxo-5,12-dihydrochrysofluorene (IV, R = OH). The ultraviolet spectrum of this product (λ_{max} 2,550; 2,900; 3,500 Å, ϵ_{max} 15,100; 13,800, 11,300) is very similar to that of the diketone (IV, R = CH_3CO), and as the infrared spectrum shows that it contains only one carbonyl group (highly conjugated, band at 1640 cm.$^{-1}$) and one hydroxyl group (band at 3585 cm.$^{-1}$), it is clear that the sterically hindered —CH(OH)— group of the neomethine derivative resists oxidation. Unlike other neomethine derivatives this substance resists dehydration on heating with formic acid, the product of the reaction being the formate ester, and doubtless this may be attributed to the fact that the driving force behind the other dehydrations in the neomethine series, the establishment of a new aromatic system, is absent in this case.



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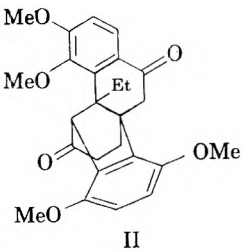

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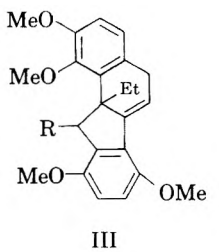

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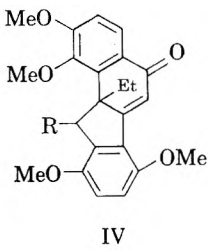

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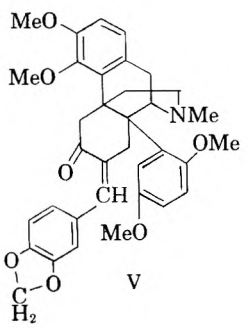

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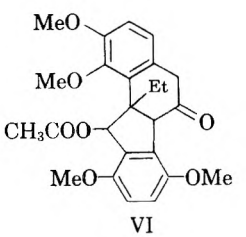

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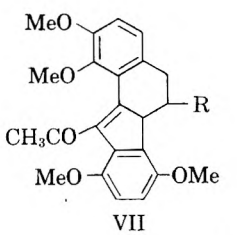

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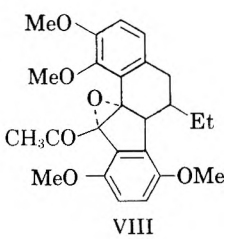

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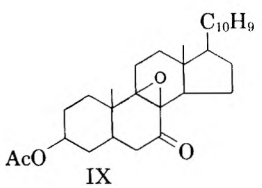

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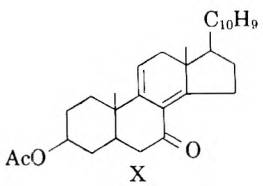

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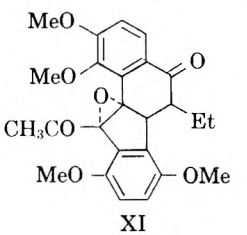


XI

The allocation of structures of two compounds in the flavothebaone series, namely Compound-E (VII, R = CH=CH_2) and dihydro-Compound-E (VII, R = Et),[6] rests on rather scanty evidence, and these structures have been further probed by the oxidation of dihydro-Compound-E. Oxidation of this substance, $C_{25}H_{28}O_6$, with either peroxytrifluoroacetic acid, or with chromic acid, affords dihydro-Compound-E_1, $C_{25}H_{28}O_6$, which no longer shows stilbenoid absorption (λ_{max} 2,900 Å, ϵ_{max} 5,020), and contains a saturated carbonyl group (infrared band at 1708 cm.$^{-1}$) in place of the unsaturated carbonyl group of the starting material; this confirms the view that the stilbenoid and α,β-unsaturated ketone double bonds of Compound-E and dihydro-Compound-E are one and the same. In addition the marked change in optical rotation is going from dihydro-Compound-E ($[\alpha]_D$ −68°) to dihydro-Compound-E_1 ($[\alpha]_D$ + 248°) suggests the establishment of new centers of dissymmetry in the latter, and this compound is accordingly formulated as (VIII). In the steroid field α,β-unsaturated ketones are known to afford epoxides by chromic acid oxidation as well as by oxidation with peracids,[7,8] and in this field epoxides between fully substituted carbon atoms are much more stable than other sorts of epoxides. For example Staveley and Bollenback[9] found, in the course of studies on α-spinasterol, that the epoxide (IX) is stable to boiling acetic acid, although it is dehydrated to (X) by heating with hydrochloric acid and acetic acid. The epoxide (VIII), however, was found stable to acid and base-catalysed dehydration. Further, epoxides such as (IX) do not react with the normal ketonic reagents due to steric hindrance

(6) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 409 (1957).

(7) O. Rosenheim and H. King, *Nature*, **139**, 1015 (1937).

(8) V. Petrow, *J. Chem. Soc.*, 998 (1939).

(9) H. E. Staveley and G. N. Bollenback, *J. Am. Chem. Soc.*, **65**, 1600(1943).

of the carbonyl group by the oxide ring,[7,8] and in agreement with the formulation (VIII), dihydro-Compound-E_1 fails to give an oxime or a dinitrophenylhydrazone.

Further oxidation of dihydro-Compound-E_1 with chromic acid yields the diketone dihydro-Compound-E_2, $C_{25}H_{26}O_7$, (XI) which contains one saturated and one aromatic carbonyl group (infrared bands at 1702 and 1675 $cm.^{-1}$) and forms a mono-2,4-dinitrophenylhydrazone. The satisfactory accommodation of these facts on the basis of the structure (VII, R = Et) for dihydro-Compound-E may be regarded as strong support for this formulation, and hence for the structure (VII, R = $CH{=}CH_2$) for Compound-E.

EXPERIMENTAL

Oxidation of flavothebaone trimethyl ether hexahydrodesazamethine. A solution of chromium trioxide (2 g.) in 90% acetic acid (8 ml.) was slowly added to a cooled solution of flavothebaone trimethyl ether hexahydrodesazamethine (5 g.) in acetic acid (40 ml.). A brown precipitate rapidly formed and the mixture was heated for 20 min. on the steam bath, when a deep green solution was obtained. Water was added and the precipitated product (4.8 g.) was collected and washed with 2*N* sodium carbonate solution and then with water. Recrystallization of the product from methanol afforded 10-*oxoflavothebaone trimethyl ether hexahydrodesazamethine* (II) as white prisms, m.p. 219–220°, $[\alpha]_D^{21}$ +174° ($CHCl_3$, c. 0.43).

Anal. Calcd. for $C_{26}H_{28}O_6$: C, 71.4; H, 6.5. Found: C, 71.3; H, 6.7.

The *dioxime*, prepared by heating a solution of the diketone, hydroxylamine hydrochloride, and sodium acetate in 80% ethanol, was obtained as white prisms, m.p. 255°, on recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{30}O_6N_2$: C, 66.8; H, 6.5; N, 6.0. Found: C, 66.1; H, 6.5; N, 5.9.

Oxidation of flavothebaone trimethyl ether dihydrodesaza-ψ-methine. (a) *With chromic acid.* A solution of chromium trioxide (0.8 g.) in 90% acetic acid (8 ml.) was slowly added to a cooled solution of flavothebaone trimethyl ether dihydrodesaza-ψ-methine (2 g.) in acetic acid (40 ml.). The mixture, which became deep blue, was heated for 10 min. on the steam bath, when a deep green solution was obtained. Water was added to the mixture and the product collected. After washing with sodium carbonate solution and water, the product was recrystallized from methanol, when 1.4 g. of *oxoflavothebaone trimethyl ether dihydrodesaza-ψ-methine* (IV, R = CH_3CO) was obtained as a light brown rods, m.p. 235°, $[\alpha]_D^{22}$ +350° ($CHCl_3$, c. 0.94).

Anal. Calcd. for $C_{25}H_{26}O_6$: C, 71.1; H, 6.2. Found: C, 70.7; H, 6.3.

The *dioxime*, prepared from the diketone and hydroxylamine hydrochloride in ethanol and pyridine, was obtained as white prisms, m.p. 261° (dec.), $[\alpha]_D^{23}$ +436° ($CHCl_3$, c. 0.84), on recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{28}O_6N_2$: C, 66.3; H, 6.2; N, 6.2. Found: C, 65.8; H, 6.2; N, 5.8.

(b) *With peroxytrifluoroacetic acid.* Trifluoroacetic anhydride (3.0 g.) was added slowly, with shaking, to a cooled suspension of 87% hydrogen peroxide (0.44 ml.) in methylene chloride (4 ml.). Disappearance of the hydrogen peroxide phase indicated the completion of the formation of the peracid. The resulting solution was added to flavothebaone trimethyl ether dihydrodesaza-ψ-methine (2.5 g.) in methylene chloride (10 ml.) over a period of 10 min. The exothermic reaction was moderated by ice-bath cooling and the dark green-blue solution was kept for 10 min. after the final addition of peracid. An equal volume of chloroform was then added to the reaction mixture and the solution washed successively with water, 2*N* sodium carbonate solution, and aqueous sodium chloride. The dried solution was then evaporated to dryness. The residual dark tar was dissolved in benzene and the solution chromatographed on alumina; a bright orange band was eluted with benzene. Evaporation of the eluate and recrystallization of the residue from methanol afforded 0.08 g. of a compound believed to be *11-acetoxy-12-ethyl-1,2,7,8-tetramethoxy-6-oxo-5,6,12,13-tetrahydrochrysofluorene* (VI) as pale brown prisms, m.p. 232°, $[\alpha]_D^{20}$ −231° ($CHCl_3$, c. 0.28).

Anal. Calcd. for $C_{25}H_{28}O_7$: C, 68.1; H, 6.4. Found: C, 67.8; H, 6.3.

Oxidation of flavothebaone trimethyl ether dihydrodesazaneomethine. A solution of chromium trioxide (0.9 g.) in 90% acetic acid (8 ml.) was slowly added to a cooled solution of flavothebaone trimethyl ether dihydrodesazaneomethine (2.3 g.) in acetic acid (100 ml.). After 10 min. the mixture was heated at 60° for 5 min., when a deep green solution was obtained. Water was then added and the product collected, washed with sodium carbonate and water, and recrystallized from methanol, when *oxoflavothebaone trimethyl ether dihydrodesazaneomethine* (IV, R = OH) was obtained as pale yellow prisms, m.p. 193–194°, $[\alpha]_D^{23}$ +219° ($CHCl_3$ c. 0.76).

Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.7; H, 6.1. Found: C, 69.7; H, 6.2.

Attempted dehydration of oxoflavothebaone trimethyl ether dihydrodesazaneomethine. A solution of oxoflavothebaone trimethyl ether dihydrodesazaneomethine (0.5 g.) in acetic anhydride (6 ml.) and 100% formic acid (3 ml.) was heated under reflux for 3 hr., during which time the solution turned deep red. Water was added to the reaction mixture and the precipitated product was collected and recrystallized from ethanol, when the *formate ester* of oxoflavothebaone trimethyl ether dihydrodesazaneomethine was obtained as pale brown plates, m.p. 252° (dec.), $[\alpha]_D^{20}$ +418° ($CHCl_3$, c. 0.44).

Anal. Calcd. for $C_{24}H_{24}O_7$: C, 67.9; H, 5.7. Found: C, 67.6; H, 5.6.

Oxidation of dihydro-compound-E. (a) *With peroxytrifluoroacetic acid.* A solution of peroxytrifluoroacetic acid, prepared from trifluoroacetic anhydride (1.6 g.) and 87% hydrogen peroxide (0.24 ml.), in methylene chloride was slowly added with constant shaking to a solution of dihydro-Compound-E (2 g.) in methylene chloride (6 ml.), the exothermic reaction being moderated by ice-bath cooling. The deep violet solution was allowed to stand for 5 min. in the ice bath after the final addition of peracid, then poured into water (25 ml.) and chloroform (20 ml.) added. The organic layer was separated and washed well with aqueous sodium carbonate, aqueous sodium dithionite (this changed the color from violet to light orange), and water. The dried solution was evaporated to dryness and the residue crystallized from methanol. Recrystallization from the same solvent afforded *dihydro-Compound-E_1* (VIII) as white prisms m.p. 193–194°, $[\alpha]_D^{20}$ +248° ($CHCl_3$, c. 0.6).

Anal. Calcd. for $C_{25}H_{28}O_6$: C, 70.7; H, 6.7. Found: C, 70.7; H, 6.8. This substance could not be induced to form an oxime or a dinitrophenylhydrazone.

(b) *With chromic acid.* A solution of chromium trioxide (0.07 g.) in 90% acetic acid (4 ml.) was slowly added to a solution of dihydro-Compound-E (0.3 g.) in acetic acid (12 ml.). A deep red solution was obtained; this was kept for 10 min. at room temperature, and then heated on the steam bath for 20 min. The product was precipitated with water, collected, and recrystallized from methanol, when 0.13 g. of dihydro-Compound-E_1 was obtained as white prisms, m.p. 193–194°, alone or mixed with the product of the peracid oxidation; $[\alpha]_D^{20}$ +243° ($CHCl_3$, c. 0.45).

This compound was recovered unchanged after boiling for

4 hr. with 100% formic acid, and after boiling for 4 hr. with potassium hydroxide in ethanol and in 2-ethoxyethanol.

Further oxidation of dihydro-Compound-E_1. Dihydro-Compound-E_1 (1 g.) in acetic acid (30 ml.) was oxidized with a solution of chromium trioxide (0.4 g.) in 90% acetic acid (4 ml.). The product was precipitated with water and recrystallized from ethanol, when 0.4 g. of *dihydro-Compound-E_2* (XI) was obtained as white prisms, m.p. 224°, $[\alpha]_D^{20}$ +304° ($CHCl_3$, c. 0.60).

Anal. Calcd. for $C_{25}H_{26}O_7$: C, 68.5; H, 6.0. Found: C, 68.5; H, 6.0.

The *2,4-dinitrophenylhydrazone* was obtained as red needles, m.p. 261° on recrystallization from a mixture of ethanol and chloroform.

Anal. Calcd. for $C_{31}H_{30}O_{10}N_4$: C, 60.2; H, 4.9; N, 9.1. Found: C, 59.9; H, 4.7; N, 8.9.

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LXXXV.[1] Synthesis of 4-Methyl and 4,4-Dimethyl Hormone Analogs[2]

H. J. RINGOLD AND G. ROSENKRANZ

Received December 13, 1956

4,4-Dimethyl-Δ^5-androsten-3-one derivatives have been prepared by alkylation of testosterone and 17α-methyltestosterone. The dihydroallo compounds are derived by catalytic hydrogenation of the Δ^5-3-ones while the corresponding 3β,17β-diols are obtained by borohydride reduction of the saturated and unsaturated ketones. Evidence is presented for the stereochemical course of catalytic and of hydride reduction, and molecular rotation discrepancies are discussed. 4-Methyltestosterone has been synthesized by alkaline cyclization of the reaction product of ethyl Grignard reagent and the enol lactone derived from ozonolysis of testosterone.

While the 4,4-dimethyl moiety is common in the triterpene series (*e.g.* lanosterol, euphol and β-amyrin) the only such steroidal compounds known have been just recently synthesized in the cholesterol[3] and ergosterol[4] series. As part of a broad program directed towards the correlation of steroid structure with activity we have had occasion to prepare a number of novel 4,4-dimethyl substituted androgen analogs as well as 4-methyltestosterone.

Treatment of testosterone (Ia) and 17α-methyltestosterone (Ib) with excess potassium *tert*-butoxide and methyl iodide in *tert*-butanol for several hours at room temperature[5] led in *ca.* 70% yield to 4,4-dimethyl-Δ^5-androsten-17β-ol-3-one (IIa) and to 4,4,17-trimethyl-Δ^5-androsten-17β-ol-3-one (IIb). These unsaturated ketones, in methanol solution, were smoothly hydrogenated at 25° and atmospheric pressure over a palladium-carbon catalyst to the corresponding dihydroallo derivatives, 4,4-dimethyldihydrotestosterone (IIIa) and 4,4,17-trimethyldihydrotestosterone (IIIb). Sodium borohydride reduction of the Δ^5-3-ketones (IIa and IIb) and of the 3-keto dihydro compounds (IIIa and IIIb) led in high yield to the respective Δ^5-3β-ols (IVa and IVb) and to the saturated 3β-ols (Va and Vb). Alternately, the saturated alcohol Va was prepared by catalytic hydrogenation of 4,4-dimethyl-Δ^5-androstene-3β,17β-diol (IVa), establishing that, as one would expect, reduction of the 5,6-double bond followed the same stereochemical course in the case of both the 3-ketone and the 3β-alcohol and further, hydride reduction of the 3-ketone led to the 3β-ol in the saturated as well as the unsaturated series.

Although, to our knowledge, there are no literature reports of the double bond hydrogenation of a steroidal Δ^5-3-ketone, the rings A/B *trans* configuration may be assigned to compounds III and V with certainty based on the following considerations: (1) catalyst absorption on the α-face of C-5,6 (which would lead to the A/B *trans* compound) is not sterically hindered, while the combination of a C-4β-axial methyl and a C-10 angular methyl group markedly hinders β-face approach to C-5,6; (2) the rotatory dispersion curves of IIIa and IIIb are identical with those of authentic 4,4-dimethyl-3-keto-A/B *trans* terpenes;[6] and (3) in all cases hydrogenation of a steroid Δ^5-3β-alcohol leads to the A/B *trans* compound.[7] That the alcohols IV and V are indeed the 3β (equatorial) alcohols follows from the recorded[3] lithium alumi-

(1) Paper LXXXIV, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(2) Presented at the 129th Meeting of the American Chemical Society, Dallas, Tex., April 1956.

(3) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

(4) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 2998 (1955).

(5) These reaction conditions are those reported by Woodward, Barton, and co-workers, reference 3, in their elegant conversion of cholesterol to lanosterol.

(6) We are grateful to Professor C. Djerassi for the determination of rotatory dispersion curves of these compounds. For a description of this useful technique, see C. Djerassi, E. W. Folz, and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).

(7) *e.g.* The hydrogenation of cholesterol leads exclusively to cholestanol [R. Willstätter and E. W. Mayer, *Ber.*, **41**, 2199 (1908)], and that of dehydroepiandrosterone to androstan-3β-ol-17-one [A. Butenandt, H. Dannenberg, G. Hanisch, and H. Kudszus, *Z. physiol. Chem.*, **237**, 57 (1935)].

num hydride reduction of the cholesterol series analog, 4,4-dimethyl-Δ^5-cholesten-3-one to the 3β-ol; arguing strictly from the steric viewpoint, hydride attack on the C-3 carbonyl from the β-face, which would be necessary for 3α-ol formation, is prevented in the compounds with or without a C-5 double bond by the steric interference of the C-4β-methyl group. Acceptance of the A/B *trans* configuration for III further necessitates the 3β-alcohol configuration for IV and V in view of the stereospecific hydride reduction of 4,4-dimethyl-3-keto-A/B *trans* terpenes to the 3β-alcohols.[8]

mal. Compounds III, with the greatest molecular rotation contributions, exhibit marked interaction between the 4β-methyl and C-10 angular methyl groups. The alcohols IV and V, with intermediate ΔM_D, do not show methyl-methyl interference, but in each case free rotation of the 3β-hydroxyl group is restricted by the 4β-methyl group, and further, in compound V, the 4β-methyl and the C-6-methylene groups are in severe interaction. Thus it would appear that in this series molecular rotation discrepancies may be correlated to steric interference factors with a fair degree of success.

TABLE I

MOLECULAR ROTATION DIFFERENCES OF 4,4-DIMETHYL STEROIDS

Substance	$[M]_D$	ΔM_D (parent compound)	
Δ^5-Cholestenone[a,b]	−10		
4,4-Dimethyl-Δ^5-cholestenone[b,c]	+4	+14	
Δ^5-Androsten-17β-ol-3-one acetate[d]	−101		Δ^5-3-Ketone
4,4-Dimethyl-Δ^5-androsten-17β-ol-3-one acetate (IIa acetate)	−104	−3	
Androstan-17β-ol-3-one[e]	+93		
4,4-Dimethylandrostan-17β-ol-3-one (IIIa)	−38	−131	Saturated 3-Ketone
17α-Methylandrostan-17β-ol-3-one[f]	+18		
4,4,17α-Trimethylandrostan-17β-ol-3-one (IIIb)	−116	−134	
Cholesterol[b,g]	−152		
4,4-Dimethylcholesterol[b,c]	−265	−113	
Δ^5-Androstene-3β,17β-diol[e]	−145		Δ^5-3β,17β-diol
4,4-Dimethyl-Δ^5-androstene-3β,17β-diol (IVa)	−261	−116	
17α-Methyl-Δ^5-androstene-3β,17β-diol[h]	−222		
4,4,17α-Trimethyl-Δ^5-androstene-3β,17β-diol (IVb)	−332	−110	
Androstane-3β,17β-diol[e]	+12		
4,4-Dimethylandrostane-3β,17β-diol (Va)	−51	−63	Saturated 3β,17β-diol
17α-Methylandrostane-3β,17β-diol[f]	−31		
4,4,17α-Trimethylandrostane-3β,17β-diol (Vb)	−94	−63	

[a] L. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953). [b] Rotation determined in chloroform (all others are in ethanol solution). [c] Reference 3. [d] H. Butenandt and G. Hanisch, *Ber.*, **69**, 2773 (1936). [e] Reference 13, p. 375. [f] Determined in these laboratories. [g] R. Anderson, *J. Biol. Chem.*, **71**, 407 (1926–27). [h] K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1939).

Inspection of molecular rotation differences (Table I) indicates a striking agreement in the cholestane, androstane and 17α-methylandrostane series. However, the rotatory contribution of a 4,4-dimethyl grouping is by no means constant. While the ΔM_D in going from the Δ^5-3-ketones to the corresponding 4,4-dimethyl compounds (II) is practically nil (+14 in the cholestene and −3 in the androstene series), the 4,4-dimethyl contribution rises to a value of about −60 in the saturated 3β-alcohols (Va and Vb), −110 in the Δ^5-3β-ol case (IVa, IVb and 4,4-dimethylcholesterol) and −130 in the 3-keto dihydroallo cases (IIIa and IIIb).

Inspection of molecular models reveals that only in the case of the 4,4-dimethyl-Δ^5-3-ketones (II) there is no steric interference of the 4β-methyl group with other groups in ring A; in these compounds the ΔM_D of the 4,4-dimethyl group is mini-

Efforts to prepare 4-methyltestosterone (IX) by modification of the direct methylation of testosterone were unrewarding and only trace amounts of the desired 4-monomethyl derivative were isolated. Compound IX was prepared in reasonable over-all yield (*ca.* 20% from testosterone) by the following reaction sequence.[9,10] Keto-acid VI from the ozonization of testosterone,[11a,b] was converted to the enol lactone (VII)[12] by heating with acetic anhydride and sodium acetate. Addition of ethyl Grignard reagent to the enol lactone followed by alkaline cyclization of the presumed intermediate VIII

(8) *Inter al.* "Reduction of Polyporenic Acid C", A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); "Pinicolic Acid A," J. Guider, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 4471 (1954); "Methyl Dihydroelemolate," T. G. Halsall, G. D. Meakins, and R. Swayne, *J. Chem. Soc.*, 4139 (1953).

(9) This reaction scheme is one that was utilized by Professor E. R. H. Jones in the preparation of 4-methylcholestenone (private communication). We are grateful to Professor Jones for having provided us with a copy of his experimental details.

(10) F. Sondheimer and Y. Mazur (private communication from Dr. F. Sondheimer) have independently synthesized 4-methylcholestenone, testosterone, and progesterone, by this identical series of reactions.

(11) (a) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938); (b) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954).

(12) G. I. Fujimoto, *J. Am. Chem. Soc.*, **73**, 1856 (1951).

gave 4-methyltestosterone (IX). The ultraviolet absorption maximum of IX at 250 mμ is in good agreement with the predicted[13] 10-mμ bathochromic shift for an α-alkyl substituent on an α,β-unsaturated keto system.

In preliminary assays[14] in the immature castrate rat, 4-methyltestosterone, by the subcutaneous route, exhibited 40% of the androgenic and 120% of the myotrophic activity of testosterone.

EXPERIMENTAL[15]

4,4-Dimethyl-Δ⁵-androsten-17β-ol-3-one (IIa). To the solution of potassium *tert*-butoxide prepared from 8 g. of potassium and 400 cc. of *tert*-butanol, 20 g. of testosterone (Ia) was added under nitrogen and the mixture stirred until the steroid had dissolved. Methyl iodide (26 ml.) was added over a period of 10 min. to the yellow solution and the reaction vessel was stoppered under nitrogen and allowed to stand for 4 hr. without external cooling or heating. Water (300 cc.) was added, the *tert*-butanol removed *in vacuo* and the resultant crystalline suspension cooled and filtered. Recrystallization from acetone furnished 15 g. (68%) of pure IIa, m.p. 198–201°, $[\alpha]_D$ −10°, no highly selective ultraviolet absorption; infrared carbonyl absorption at 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.67; H, 10.19. Found: C, 80.05; H, 10.28.

The acetate of IIa (acetic anhydride–pyridine, recrystallization from methanol) exhibited m.p. 154–156°, $[\alpha]_D$ −29°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.00; H, 9.34.

4,4,17-Trimethyl-Δ⁵-androsten-17β-ol-3-one (IIb). Methyltestosterone (Ia) when treated exactly as above gave the 4,4-dimethyl compound IIb in 78% yield, m.p. 194–196°, $[\alpha]_D$ − 32°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.36. Found: C, 80.05; H, 10.57.

4,4-Dimethylandrostan-17β-ol-3-one (IIIa). The unsaturated ketone IIa (1 g.), in 30 cc. of methanol was hydrogenated at 25° and 1 atmosphere pressure over 500 mg. of prehydrogenated 10% palladium-carbon catalyst. Hydrogen uptake ceased in 4.5 hr. after the absorption of 92 cc. (theoret. 99 cc.), the filtered solution was taken to dryness and the residue crystallized from acetone-hexane to yield 0.82 g. of 4,4-dimethyldihydrotestosterone (IIIa), m.p. 140–146°. The analytical sample, from the same solvent, melted at 145–147°, $[\alpha]_D$ −12°, infrared carbonyl maximum at 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.97; H, 10.69.

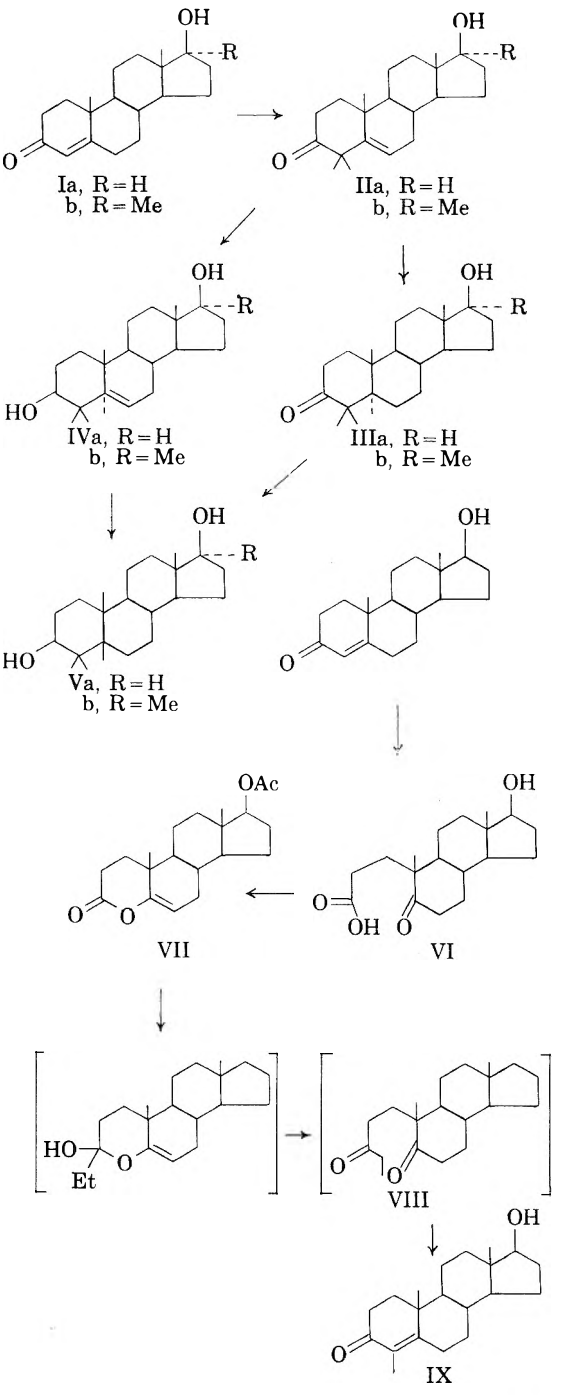
4,4,17-Trimethylandrostan-17β-ol-3-one (IIIb). Hydrogenation of 1 g. of IIIa as above (97 cc. hydrogen uptake in 5.5 hr.) and crystallization from acetone gave 600 mg. of 4,4,17-trimethyldihydrotestosterone (IIIb), m.p. 183–185°, $[\alpha]_D$ −35°.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.75; H, 11.05.

4,4-Dimethyl-Δ⁵-androstene-3β,17β-diol (IVa). A solution of 1 g. of sodium borohydride in 2.5 cc. of water was added to 2 g. of IIa in 40 cc. of tetrahydrofuran, the mixture boiled for 1 hr. and the solvent finally removed *in vacuo*. Cold water (25 cc.) was added, the excess hydride decomposed by dropwise addition of glacial acetic acid (2 cc.), the crude IVa filtered, thoroughly washed with water, dried, and recrystallized from acetone, yielding 1.8 g. of 4,4-dimethyl-Δ⁵-androstene-3β,17β-diol, m.p. 213–217°. The analytical sample from acetone exhibited m.p. 216–218°, $[\alpha]_D$ −82°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.99; H, 10.48.

4,4,17-Trimethyl-Δ⁵-androstene-3β,17β-diol (IVb). Sodium borohydride reduction of IIb as described above for IIa gave a 90% yield of 4,4,17-trimethyl-Δ⁵-androstene-3β,17β-diol (IVb), m.p. 212–217°. Analytical sample (acetone), m.p. 216–220°, $[\alpha]_D$ −100°.



(13) See L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Third Edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 190–192.

(14) Bioassays by the Endocrine Laboratories, Madison, Wis.

(15) Melting points are uncorrected. Unless specified otherwise, rotations and ultraviolet absorption spectra were determined in ethanol and infrared spectra in chloroform solution. Thanks are due Mrs. E. Necoechea and A. Mijares for their able technical assistance and to A. Erlin for determination of rotations and spectra.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.20; H, 10.64.

4,4-Dimethylandrostane-3β,17β-diol (Va). (*a*) *By borohydride reduction of* IIIa. Sodium borohydride reduction of saturated ketone IIIa by the usual procedure furnished in 88% yield, 4,4-dimethylandrostane-3β,17β-diol (Va), m.p. 245–247°, $[\alpha]_D$ −16°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.68; H, 11.01.

(*b*) *By catalytic hydrogenation of* IVa. The hydrogenation at 25° and atmospheric pressure of 300 mg. of IVa in 15 cc. of methanol over 150 mg. of 10% prereduced palladium-carbon was complete after 2 hr., with 33 cc. hydrogen uptake (theoret. 30 cc.). Crystallization of the crude product from acetone gave 210 mg. of Va, m.p. 245–247°, identical in all respects with the product obtained by hydride reduction of IIIa.

4,4,17-Trimethylandrostane-3β,17β-diol (Vb). The trimethyldiol (Vb) was derived in 87% yield by sodium borohydride reduction of IIIb in aqueous tetrahydrofuran solution. The analytical sample from acetone melted at 230–234°, $[\alpha]_D$ −28°.

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 79.14; H, 11.56.

Keto Acid (VI). The keto acid VI, m.p. 200–202°, was prepared in 76% yield by ozonization of testosterone as described by Weisenborn, Remy, and Jacobs.[11b]

Enol Lactone (VII). A mixture of 5 g. of VI and 5 g. of sodium acetate was heated in 125 cc. of boiling acetic anhydride for 21 hr. The solvent was removed *in vacuo*, ice water was added, the mixture extracted with ethyl acetate, the organic phase washed with cold 1% potassium carbonate solution and evaporated to dryness. Crystallization of the residue from hexane gave 4.6 g. (85%) of enol lactone (VII), m.p. 125–130°, which was used without further purification. Fujimoto[12] reports m.p. 129–133° for an analytical specimen of VII.

4-Methyltestosterone (IX). A stirred solution of 3 g. of enol lactone (VII) in 40 cc. of anhydrous ether and 10 cc. of anhydrous tetrahydrofuran was treated dropwise, at 0°, with 4 cc. of a 3*N* ethereal solution of ethyl magnesium bromide. The mixture, under nitrogen, was stirred for 1.5 hr. at ice bath temperature, at 25° for an additional 16 hr. and finally poured into ice water and acidified with dilute hydrochloric acid. The ether extract, after successive washing with 4*N* hydrochloric acid, water, 2% sodium bicarbonate and water, was taken to dryness, the residue dissolved in 260 cc. of methanol and a solution of 9 g. of sodium hydroxide in 45 cc. of water was added. The solution, after 3 hr. of boiling under nitrogen, was neutralized with acetic acid, concentrated to a volume of *ca.* 50 cc., poured into water, the steroid extracted with ethyl acetate, and the ethyl acetate extract washed with water and evaporated to dryness.

The product, dissolved in 200 cc. of benzene, was subjected to chromatographic purification on a column of 150 g. of alkaline alumina. Pooling of the crystalline benzene-ether fractions (8:2) and recrystallization from acetone-hexane gave 730 mg. (27%) of 4-methyltestosterone (IX), m.p. 169–171°, $[\alpha]_D$ +121° (chloroform), λ_{max} 250 mμ, log ε 4.21, infrared carbonyl absorption band at 1660 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.45; H, 10.10.

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[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

Reactivity Studies on Natural Products. II.[1] Kinetics of Bromination of Some Steroid Ketones

OWEN H. WHEELER AND J. L. MATEOS

Received November 19, 1956

The rates of bromination of cholestan-3-one, coprostan-3-one, 6- and 7-ketocholestane, and, for comparison, cyclopentanone and cyclohexanone, have been measured in 90% acetic acid containing 0.06*M* hydrogen chloride The results show that both the rate-determining enolization and the approach of the bromine are important steps.

The reactivity of some steroid ketones toward hemiketal formation has been recently reported,[1] but no kinetic study has been made of reactions involving the enolic form of the ketone. The acid-catalyzed bromination of ketones involves enol formation as the rate-determining step,[2] and accordingly the rates of bromination of cholestan-3-one, coprostan-3-one, 6- and 7-ketocholestane, cyclopentanone and cyclohexanone, have been measured (see Table I), to investigate the influence of differences in ring fusion and ring position on ketone enolization.

It is known that 3-keto-steroids of the allo-series (rings A/B trans), *e.g.* cholestan-3-one, undergo bromination in position 2, whereas the corresponding ketones of the normal series (rings A/B cis), *e.g.*, coprostan-3-one, give the 4-bromo ke-

TABLE I

BROMINATION OF KETONES

	75% Acetic Acid[a] $k \times 10^{5b}$	90% Acetic Acid[c] $k \times 10^{5b}$	Ratio[d]
Cyclopentanone	1.91 ± 0.05	4.61 ± 0.04	0.34
Cyclohexanone	6.25 ± 0.11	13.4 ± 0.5	1.0
Cholestan-3-one		29.5 ± 0.6	2.2
Coprostan-3-one		22.6 ± 0.5	1.7
6-Ketocholestane		1.62 ± 0.02	0.12
7-Ketocholestane		0.910 ± 0.015	0.068

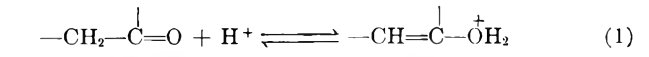
[a] Containing 0.10*M* hydrogen chloride. [b] At 25.0 ± 0.1°. [c] Containing 0.0617*M* hydrogen chloride. [d] Radio of rates in 90% acetic acid to cyclohexanone = 1.0.

(1) Part I. *Anal. Chem.*, 29, 538 (1957).

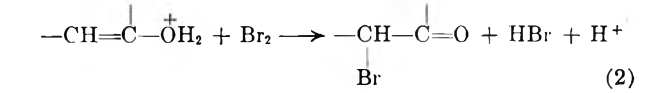
(2) (a) A. Lapworth, *J. Chem. Soc.*, 85, 30 (1904); (b) H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951).

tone.[3] Also 6-ketosteroids form 5-bromo derivatives,[4] but 7-ketosteroids give the 6-bromocompound.[5] From the present kinetic study the order of the rates of bromination was found to be cholestan-3-one > coprostan-3-one > cyclohexanone > cyclopentanone > 6-ketocholestane > 7-ketocholestane. Any detailed mechanism of bromination of cyclic ketones must explain both the differences in position of attack and the differences in rate.

The acid-catalyzed bromination of ketones has been shown to be first order in ketone, but independent of the bromine concentration,[2a] and these results have been interpreted as indicating a slow rate-determining reversible enolization of the ketone (1), followed by rapid attack of bromine (2).[6] In the



(1)



(2)

enolization of a cyclic ketone an axial hydrogen atom will be lost,[7a] since this allows of greater conjugation in the transition state. Similarly, addition of bromine to the once-formed enol will take place by axial attack which is the least hindered direction of attack upon a cyclohexene ring. An α-axial-bromo compound is always the initial product of the reaction.[7,8]

The greater reactivity of cyclohexanone as compared to cyclopentanone is consistent with the smaller extent of enol formation of the latter,[9] and with the generalization[10] that reactions proceed in such a manner as to favor retention of a double bond exocyclic to a five-membered ring and to avoid retention of a double bond exocyclic to a six-membered ring. In the case of cholestan-3-one, bromination takes place in position 2,[3,11] since there is greater hyperconjugative stabilization of the 2,3 double bond with respect to the 3,4 double bond,[12a] and smaller crowding between the C-10 angular methyl group and the axial hydrogen atoms at C-6[12c] with the former double bond. Moreover, formation of the 2,3 enol bends the hydrogen atom at C-2 away from the angular methyl group at C-10, and enolization will reduce the non-bonded interactions present in the present ketone, and the rate of bromination will be greater than that of cyclohexanone. Similarly, enol formation in the 3,4 position of coprostan-3-one[11] reduces the non-bonded interactions of the equatorial hydrogen atom at C-4 with the axial hydrogen atoms on carbons 7 and 9,[12a] whereas introduction of a Δ^2-double bond only reduces interactions on C-3 and C-9. This reduction of the non-bonded interactions also gives an enhanced rate of bromination.

A steroid 6-keto group can enolize by losing either the tertiary axial hydrogen atom at C-5 or a secondary hydrogen atom from C-7, but the rate of loss of a tertiary hydrogen atom will be much greater, and bromination will take place in position -5. However, introduction of this double bond will produce strain in both rings A and B, since all bond angles are slightly distorted[12c] and also the attack of a solvent molecule to remove the proton during enolization[2b] will be hindered by the axial hydrogen atoms at C-3 and C-7. For these reasons the observed rate of bromination is much less than that of cyclohexanone. In contrast to cholestan-3-one and coprostan-3-one, where enolization reduces the strain in the parent ketone, in the case of 6-ketocholestane enolization considerably increases the strain in the system.

For the 7-ketone enolization can again take place in two directions, involving either the tertiary axial hydrogen atom at C-8, or a secondary hydrogen atom at C-6. Loss of a tertiary hydrogen atom is generally more favored, but in this case approach from the top side of a solvent molecule to the axial hydrogen atom at C-8, and subsequent attack of the large bromine atom on the once-formed enol is impeded by the angular methyl groups on C-10 and C-13, and hence reaction will involve the 6,7 enol.[13] Thus for steric reasons bromination will take place

(3) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1854 (1935); A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); A. Butenandt, G. Schramm, A. Wolff, and H. Kudszus, *Ber.*, **69**, 2779 (1936); L. Ruzicka, W. Bosshard, W. H. Fischer, and H. Wirz, *Helv. Chim. Acta*, **19**, 1147 (1936).

(4) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937); I. M. Heilbron, J. Jackson, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 102 (1938); R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).

(5) T. Barr, I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.* 334 (1938); D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 1064 (1956).

(6) *Cf.* C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 536. J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, N. Y., 1956, p. 198.

(7) (a) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954); (b) D. A. H. Taylor, *Chemistry & Industry*, 250 (1955).

(8) The ketonization of enols has also been shown to proceed by addition of a proton from the least hindered side. H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); *J. Amer. Chem. Soc.*, **78**, 1168 (1956).

(9) G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 656, 669, (1947).

(10) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(11) Cholestan-3-one also forms Δ^2 enol acetates and ethers, whereas coprostan-3-one forms the Δ^3 derivatives. W. G. Dauben, R. A. Micheli, and S. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952); M. Ruben and B. H. Armbrecht, *J. Am. Chem. Soc.*, **75**, 3513 (1953); H. H. Inhoffen, W. Becker and G. Kolling, *Ann.*, **568**, 181 (1950); H. H. Inhoffen, G. Kolling, G. Koch, and I. Nebel, *Ber.*, **84**, 361 (1951).

(12) (a) D. A. H. Taylor, *Chemistry & Industry*, 250 (1954); (b) A. S. Dreiding, *Chemistry & Industry*, 1419 (1954); (c) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

(13) The Δ^6-enol acetate is also formed. R. Hirschmann and N. C. Wendler, *J. Am. Chem. Soc.*, **75**, 2361 (1953).

in position 6,[14] and at a reduced rate since an equilibrium will exist between the two enols, which will favor the Δ^7 isomer. The small difference between the tertiary bromination of the 6-ketone and secondary bromination of the 7-ketone must be due to the fact that the Δ^6 double bond, in contrast to a Δ^5 double bond, introduces little strain in ring A. The 7- position is unique in its steric environment. An 11-ketone gives normally a 9-bromo derivative[15a] and $\Delta^{9(11)}$-enol acetate,[14, 15b] since approach to the underside of the molecule is not hindered.

EXPERIMENTAL

Ketones. These were highly purified specimens which had been prepared in a previous study.[1]

Solvents. Acetic acid (Baker Analyzed) was refluxed with and fractionated from chromium trioxide and acetic anhydride, and the fraction boiling at 107–108°/580 mm. was used. Acetic acid (1.8 l.) was diluted with distilled water to 2 l. and the solvent had d_4^{25} 1.0487. Hydrogen chloride, generated from analytical grades of hydrochloric and sulfuric acids, was passed into a portion of this acetic acid solution to give a 0.6171*M* solution. The hydrogen chloride was determined by adding aliquots to dilute nitric acid containing excess silver nitrate and titrating the excess silver nitrate with potassium thiocyanate. Bromine (Baker Analyzed) was added to the hydrochloric-acetic acid solution to about 0.05*M*. Its concentration was determined before each experiment, as described below.

A weighed quantity of ketone (0.2–0.3 g.) was dissolved in 90% acetic acid (*ca.* 80 ml.) in a 100 ml. graduated flask and allowed to equilibrate in temperature in a constant temperature bath maintained at 25.0 ± 0.1°. Ten milliliters of the stock solution of bromine were added and the volume quickly made up to the mark. Aliquots were withdrawn at various times and added to excess potassium iodide in water (*ca.* 20 ml.). The liberated iodine was titrated with sodium thiosulfate (0.05*M*), using starch as indicator.[16] Each experiment was repeated 3 or 4 times, and the rate constants for the first order reaction were obtained graphically. Linear plots were obtained up to about 60% reaction, but showed divergencies after this due to the catalytic action of the hydrogen bromide formed in the reaction, and to polybromination.[17]

Acknowledgments. This work was supported by grants from the Rockefeller Foundation, New York.

MEXICO 20, D. F.

(14) A similar steric effect has been suggested to explain the course of enol acetate formation. A. Crawshaw, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 731 (1954).

(15) (a) H. B. Henbest, E. R. H. Jones, A. A. Wagland, and T. I. Wrigley, *J. Chem. Soc.*, 2477 (1955); (b) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones and T. Walker, *J. Chem. Soc.*, 747 (1954).

(16) *Cf.* D. P. Evans, *J. Chem. Soc.*, 785 (1936).

(17) Cholestan-3-one has been shown to absorb about 3 moles of bromine during one day, followed by uptake of a fourth in 5 days. D. H. R. Barton, J. F. McGhie, M. K. Pradhan, and S. A. Knight, *J. Chem. Soc.*, 876 (1955).

[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

4,5-Epoxy-3-oxo Steroids

ROY H. BIBLE, JR., CHESTER PLACEK,[1] AND ROBERT D. MUIR

Received November 20, 1956

Several 3-keto-Δ^4 steroids have been converted to the corresponding epoxides. Both the α and the β epoxides of progesterone were isolated.[2] Fermentation of 4,5-epoxypregnane-3,20-dione (I) by *Rhizopus nigricans* led to the isolation of 4β,5-epoxy-11α-hydroxypregnane-3,20-dione. Treatment of I with formic acid gave 4-hydroxyprogesterone (IV).[3]

As the preliminary step to investigating a hypothesis[4] that biological 11β-hydroxylation proceeds through the 4,5-epoxy-3-oxo steroid, a number of the 4,5-epoxides were prepared and a few of their reactions studied.[5]

The epoxides were prepared by alkaline hydrogen peroxide oxidation of the corresponding conjugated ketones. Table I summarizes the analytical data and physical constants of these oxides. Plattner, Heusser, and Kulkarni[6] have shown that 4-

(1) Present address: American Chemical Society Applied Journals, Chicago.

(2) W. Cole and P. L. Julian [*J. Org. Chem.*, 19, 131 (1954)] described an epoxide of progesterone, m.p. 173–175°, but gave no optical rotation or details of its synthesis.

(3) H. Levy and M. L. Mednick (private communication) have independently isolated 4-hydroxyprogesterone as a by-product from the reaction of progesterone with hydrogen peroxide and osmium tetroxide and also by the acid dehydration of the 4,5-diol.

(4) The hypothesis is that formation of the 4,5-epoxide is followed by an "anomalous" opening of the oxide involving a C_{11} hydrogen. The possibility of this type of opening is suggested by the work of A. C. Cope, S. W. Fenton, and C. F. Spencer [*J. Am. Chem. Soc.*, 74, 5884 (1952)]. The resulting 4,11-dihydroxy compound then dehydrates to give the 3-keto-Δ^4-11-hydroxy compound.

(5) (a) B. Camerino, B. Patelli, and A. Vercellone have recently [*J. Am. Chem. Soc.*, 78, 3540 (1956)] described the epoxides from testosterone and the cleavage products from these oxides. (b) Since the completion of our work other groups have reported on overlapping work. See B. Camerino and B. Patelli, *Il Farmaco* (Pavia), *Ed. sci.*, 11, 579 (1956); B. Camerino, B. Patelli, A. Vercellone, and F. Media, *Il Farmaco* (Pavia), *Ed. sci.*, 11, 586 (1956); and H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz. *J. Org. Chem.*, 21, 1432 (1956).

(6) Pl. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, 31, 1822 (1948).

TABLE I

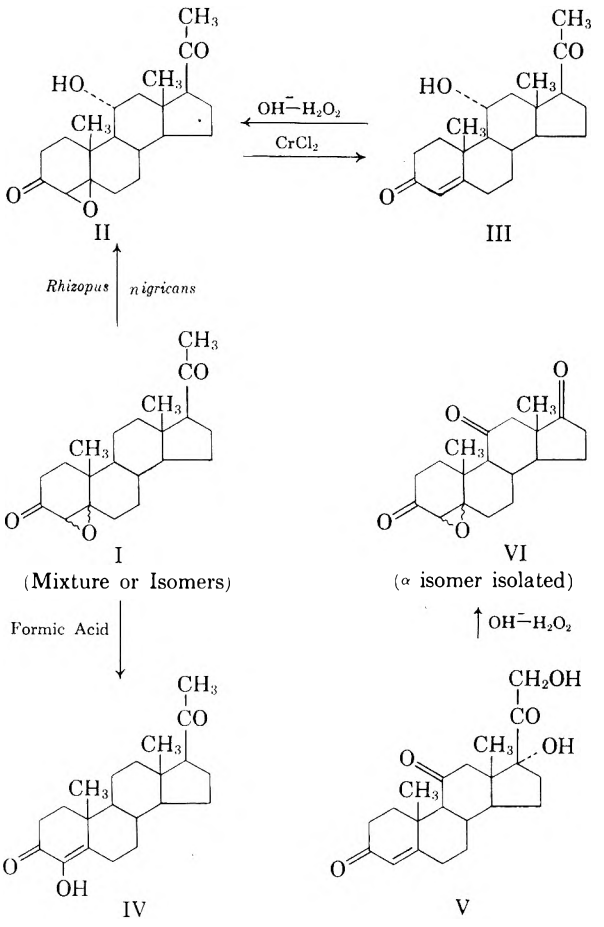
4,5-EPOXY-3-OXO STEROIDS

Starting Material	Product-epoxide isomer	Empirical Formula	M.P., °C.	$[\alpha]_D$	ΔM_D[a]	C Calcd.	C Found	H Calcd.	H Found	Recrystallized from
Adrenosterone	α	$C_{19}H_{24}O_4$	252° d.	+70°	−563°	72.13	72.10	7.65	7.69	Chloroform + methanol
	Second crop		195–225°	+190°	−189°		72.18		7.18	Acetone
4-Androstene-3,17-dione	β	$C_{19}H_{26}O_2$	200–202°	+220	+192	75.46	75.68	8.67	8.74	Aqueous methanol
	Second crop		159–163°	+117	−120		75.58		8.77	Skellysolve B + acetone
Cortisone	α of adrenosterone									
Desoxycorticosterone	β	$C_{21}H_{30}O_4$	135–140°	+204	+119°	72.80	72.81	8.73	8.61	Aqueous methanol
11α-Hydroxyprogesterone	β	$C_{21}H_{30}O_4$	156–159°	+178°	+35°	72.80	72.72	8.73	8.70	Aqueous methanol
	Second crop		118–130°	+152	−56°		72.90		8.69	Skellysolve B
Progesterone	α[b]	$C_{21}H_{30}O_3$	175–177.5°	+14.5°	−580°	76.32	75.88	9.15	9.36	Skellysolve B
	β		133–135.5°	+211°	+68°		76.06		9.33	Aqueous methanol
	Mixture			+156°	−113°		76.22		9.12	Skellysolve B
Testololactone	β	$C_{19}H_{26}O_4$	252° d.	+85°	+141°	71.67	71.56	8.23	8.44	Skellysolve B + ethanol, chloroform + methanol
	Second crop		204–240°	−52°	−295°		71.40		8.31	Acetone

[a] $\Delta M_D = M_D$ (epoxide) − M_D (conjugated ketone). The following values for the specific rotations (rounded off the nearest degree) were used: adrenosterone, +262° (ref. 12, p. 423); 4-androstene-3,17-dione, +190° (ref. 12, p. 375); desoxycorticosterone, +178° (ref. 12, p. 407); 11α-hydroxyprogesterone, +176° (ref. 14); progesterone, +200° [E. Fernholz, *Ber.*, **67**, 2027 (1934)]; testololactone, +43° [J. Fried, R. W. Thoma, and A. Klingsberg, *J. Am. Chem. Soc.*, **75**, 5764 (1953)]. ΔM_D for 4β,5-epoxycoprostan-3-one (ref. 6) was +198° taking $[\alpha]_D$ for 4-cholesten-3-one as +89 [A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935)]. In the work of Camerino, Patelli, and Vercellone (ref. 5a) the average ΔM_D for the β isomer was about +145° while for the α isomer it was about −460°. [b] See ref. 2.

cholesten-3-one is converted to the β oxide. The optical rotation which they reported for the β oxide was used as a standard in assigning the configurations given in Table I.

Cortisone (V) on treatment with alkaline hydrogen peroxide gave the epoxides of adrenosterone (VI)[7] from which the α isomer was isolated. The same compound was obtained directly from adrenosterone.



The properties of several mixtures of α and β epoxides are given in Table I. The mixture described for progesterone is the one actually employed in subsequent reactions. Based on the rotation of this material, it contained about 75% of the β epoxide and 25% of the α epoxide.

Some selected spectral data of the epoxides are given in Table II. The infrared absorption spectrum of each of the epoxides has a band between 11.56 and 11.67 μ and also a band between 12.60 and 12.68 μ. Sallmann and Tamm[8] assigned similar bands to the α,β-epoxy ketone group. A band in the 11.6 μ region has been assigned by Patterson[9] to epoxides.

The spectra (KBr disks) of the α and β epoxides of progesterone are strikingly different in the carbonyl region. The β isomer exhibits two well-defined bands (5.85 and 5.96 μ) while the α isomer displays only one band (5.84 μ, fairly broad).[10] The spectrum of the mixed epoxides ("mixture"—Table II) displays only one band even though it contains 75% of the β isomer. In chloroform solution the β isomer has a single sharp band (5.88 μ) in the carbonyl region. The spectrum of 4β,5-epoxy-11α-hydroxypregnane-3,20-dione (KBr disk) also has two carbonyl bands while the "second crop" material from the epoxidation of 11α-hydroxyprogesterone has only one.

The low-intensity ultraviolet absorption bands of the epoxy ketones are listed in Table II. Sallmann and Tamm[8] reported a bathochromic shift (from about 282 to about 300 mμ) of the six-membered cyclic ketone band on the introduction of an α,β-epoxy group. It will be seen from Table II that this shift is clearly detectable in the spectrum of the epoxide of testololactone. The spectra of the other oxides are complicated by the presence of additional keto groups.[11]

The mixture of isomeric epoxides from progesterone ([α] + 156°) on refluxing with formic acid gave 4-hydroxy progesterone (4-hydroxy-4-pregnene-3,20-dione, IV).[3] This structure was assigned on the basis of the elementary analysis, the ultraviolet absorption spectrum[12] (λ_{max} 277 mμ, log ϵ 4.06) and the infrared absorption spectrum (2.92 μ-hydroxy; 5.89 μ-C_{20} carbonyl; 6.02 and 6.16 μ-3-keto-Δ^4 system.) The molecular rotation (+585°) is consistent with that of progesterone (+628°). No evidence for the presence of any 11-hydroxylated progesterone could be found by paper chromatography of the material in the mother liquors from the formic acid reaction.

Fermentation of the mixture of isomeric epoxides from progesterone by *Rhizopus nigricans* led to the isolation of an isomerically pure hydroxylated derivative. Reduction of this fermentation product with chromous chloride[2] gave 11α-hydroxyprogesterone while treatment with hot formic acid gave a crude product having a strong absorption peak at 275 mμ. On the basis of these reactions and the molecular rotation, the fermentation product must be 4β,5-epoxy-11α-hydroxypregnan-3-one (II). The structure of this compound was confirmed by comparison with a sample of the oxide prepared by the epoxidation of 11α-hydroxyprogesterone (III).

(7) Camerino, Patelli and Vercellone (ref. 5a) indicated that they were able to isolate the epoxides of cortisone.

(8) F. Sallmann and Ch. Tamm, *Helv. Chim. Acta*, **39**, 1340 (1956).

(9) W. A. Patterson, *Anal. Chem.*, **26**, 823 (1954).

(10) It is of interest that S. Bernstein, M. Heller, and S. M. Stolar [*J. Am. Chem. Soc.*, **76**, 5675 (1954)] reported that in a Nujol mull 16α-hydroxyprogesterone displays three carbonyl bands while in chloroform it shows only the expected two bands.

(11) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(12) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, pp. 194–5.

TABLE II

SPECTRAL DATA OF THE 4,5-EPOXY-3-OXO STEROIDS

Epoxide Prepared from	Isomer	Infrared (KBr) λ_{max} (μ)				UV[a] λ_{max} (mμ)	E_{max}
Adrenosterone	α	5.77	5.85	11.65	12.68	295–298	120
	second crop	5.76	5.83	11.61	12.62		
4-Androstene-3,17-dione	β	5.73	5.83	11.58	12.63	295–298	90
	second crop	5.76	5.82	11.56	12.65		
Desoxycorticosterone	β	5.85	5.90[b]	11.57	12.62	285	80
11α-Hydroxyprogesterone	β	5.89	5.97	11.56	12.62	288–290	90
	second crop	5.91		11.58	12.60		
Progesterone	α	5.84		11.58	12.65	288–290	80
	β	5.85	5.96	11.62	12.65	286–290	110
		5.88[c]		11.60[c]			
	mixture	5.87		11.61	12.66		
Testololactone	β	5.81		11.58	12.67	298–302	40
	second crop	5.81		11.67	12.68		

[a] Determined in methanol at a concentration of about 0.4 g./l. [b] Shoulder. [c] Chloroform solution; stopped at 12.2 μ.

EXPERIMENTAL

Except where noted, rotations were determined using 0.5–1.0% chloroform solutions, infrared absorption spectra were obtained using pressed potassium bromide disks, and ultraviolet absorption spectra were run on methanol solutions. All melting points were taken on a Fisher-Johns block and are corrected.

The analytical determinations were made by the Analytical Department under Dr. Robert T. Dillon. The paper chromatography was performed by Miss Jeanette D. Mier.

4,5-Epoxides from 3-keto-Δ^4 steroids.[6] To a stirred solution of the steroid (0.015 mole) in methanol (200 ml.) were added dropwise and simultaneously 4*N* sodium hydroxide (24.4 ml.) and 30% hydrogen peroxide (24.4 ml.). The mixture was maintained at 20° during the addition. A white precipitate formed soon after the addition was begun. The resulting mixture was stored overnight at 2°. After dilution with water the mixture was extracted with benzene. The benzene solution was washed with water and then dried over anhydrous sodium sulfate. The residue remaining after distillation of the benzene was purified by recrystallization. The analytical data and physical constants of the oxides are summarized in Table I. Some selected spectral data are given in Table II.

The yields of the mixed epoxides (one recrystallization) ranged from 20 to 60%. The purification of the individual isomers required three or four recrystallizations.

4-Hydroxyprogesterone (IV).[3] A solution of I (4.86 g., $[\alpha]_D$ +156°) in formic acid (75 ml.) was refluxed for 45 min. The mixture was poured while hot into hot water (200 ml.). After the solution had cooled, the precipitate was collected and washed with water. Recrystallization from aqueous methanol gave crude 4-hydroxyprogesterone (2.41 g., m.p. 203–221°). A second recrystallization gave platelets melting at 221–227° (subl.).

A sample for analysis was obtained by sublimation (0.07 mm. pressure); m.p. 226–228° (presoftened; subl.); $[\alpha]_D$ +177° (chloroform); +185° (1% in ethanol); λ_{max}: 277 mμ (log ϵ = 4.06); 2.92, 5.89, 6.02 and 6.16 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.49, 76.69; H, 9.58, 9.47.

Paper chromatography failed to reveal any 11α- or 11β-hydroxyprogesterone in the mother liquors. Using a cyclohexane-phenyl Cellosolve system 4-hydroxyprogesterone migrates at approximately the same rate as progesterone.[13] (In 3 days the center of the spot of 4-hydroxyprogesterone moved approximately 9.4 cm. compared with 9.3 cm. for progesterone.)

(13) L. F. Fieser and R. Stevenson [*J. Am. Chem. Soc.*, 76, 1728 (1954)] reported that 4-hydroxy-4-cholesten-3-one was eluted with surprising ease from acid-washed alumina.

4β,5-Epoxy-11α-hydroxypregna-3,20-dione (*II*) *by fermentation of I.* A liquid culture medium containing a commercial enzymatic digest of whey protein, corn steep liquor and dextrose was adjusted to *p*H 4.5 with concentrated hydrochloric acid and dispensed in 400 ml. quantities in 2-l. Erlenmeyer flasks. These were plugged with nonabsorbent cotton and sterilized in an autoclave for 5 min. at 120°. After cooling to room temperature, each of 20 flasks was inoculated with 3 ml. of a suspension of spores of *Rhizopus nigricans* (ATCC 6227b) prepared from a 12-day culture of the organism on a hominy grit sporulation medium. These cultures were incubated at 25° on a rotary shaker for 24 hr., at which time each received 100 mg. of 4,5-epoxypregnane-3,20-dione (I-$[\alpha]_D$ +156) in 5 ml. of ethanol. Incubation was continued for an additional 24-hr. period. The cultures were then pooled and mycelium was separated by filtration and washed with methylene chloride.

The filtrate was extracted twice with a total of 9.6 l. of methylene chloride and the solvent fractions were pooled and concentrated under reduced pressure to a volume of about 750 ml. The concentrate was extracted once with 100 ml. of 2% sodium bicarbonate and once with 100 ml. of distilled water. The solvent was removed over a steam bath under reduced pressure. The residue (2.82 g.) was chromatographed over silica (200 g.). Elution was begun with benzene and followed with an ethyl acetate–benzene mixture. The material eluted with 25% ethyl acetate was recrystallized once from aqueous methanol; yield: 690 mg.; m.p. 156–159°; $[\alpha]_D$ +184° (1% in ethanol).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.88, 72.80; H, 9.04, 8.93.

This compound was identical (melting point, infrared and ultraviolet absorption spectra, no depression of the melting point on mixing) with 4β,5-epoxy-11α-hydroxypregnane-3,17-dione.

A sample of the oxide (40 mg.) was refluxed in formic acid (9 ml.) for 30 min. The formic acid was removed under reduced pressure. The ultraviolet absorption spectrum of the residue had a peak at 275 mμ (2.16 mg. %; optical density of 0.22).

11-Oxoprogesterone from II. A mixture of chromic chloride hexahydrate[2] (1.0 g.), 95% ethanol (12 ml.), and zinc dust (0.8 g.) was stirred for 2 hr. under carbon dioxide. The initial exothermic reaction was controlled by cooling the reaction vessel in an ice bath. The mixture was allowed to stand overnight under a slow stream of carbon dioxide. A solution of II (200 mg.) in ethanol (15 ml.) was added all at once with mixing. The color of the mixture turned from blue to green within several minutes. The reaction mixture was stirred for 30 min. and was then diluted with water. The diluted mixture was extracted with chloroform. The chloroform solution was washed with water and then dried over

sodium sulfate. Removal of the solvent under reduced pressure gave a residue which crystallized on cooling. Two recrystallizations from aqueous methanol gave colorless material (180 mg.) melting at 159–160.5°; $[\alpha]$ + 170°; λ_{max} 241 mμ (log ϵ = 4.20) (reported[14]: m.p. 166–168°; $[\alpha]_D$ +175.9°). The melting point of a sample mixed with authentic 11α-hydroxyprogesterone was 161–169°. The infrared absorption spectrum (KBr disk) of this compound was significantly different from that of 11α-hydroxyprogesterone which had been recrystallized from aqueous acetone.

The chromous chloride reduction product was oxidized with chromic anhydride in pyridine[15] to give 11-oxoprogesterone, m.p. 173.5–177.0; $[\alpha]_D$ +238° (acetone); reported[16]: m.p. 172–174°; $[\alpha]_D$ +238.5 ± 8° (acetone).

CHICAGO 80, ILL.

(14) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).

(15) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(16) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

[CONTRIBUTION FROM THE GUY AND BERTHA IRELAND RESEARCH LABORATORY, DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF NORTH DAKOTA SCHOOL OF MEDICINE]

Standard Method for Synthesis of Some 1-C^{14}-Labeled Amino Acids[1]

HERBERT J. FROMM

Received December 10, 1956

A standard, 5-step method for the synthesis of 1-C^{14}-labeled glycine, DL-alanine, and DL-leucine has been investigated. The procedure may be of practical value for the preparation of carboxyl-labeled amino acids. The technique is limited to amino acids which form phthaloyl derivatives.

It has been reported that 1-C^{14}-labeled fatty acids can be prepared by decarboxylating the silver salt of the acid with a halogen to the corresponding alkylhalide, and subsequently reversing the process with $C^{14}O_2$ in the Grignard reaction.[3]

We felt that the carboxyl-labeled amino acids could be prepared in an analogous fashion; however, the silver salts of the α-amino acids when decarboxylated with a halogen produce the corresponding alkylidenimine hydrohalides rather than the α-aminoalkylhalides.[4] It was thought that the alkylidenimine compounds may have arisen through dehydrohalogenation of the α-amino alkylhalides. Blocking of the amino group would preclude this dehydrohalogenation, and might thus permit the synthesis of 1-C^{14}-labeled amino acids *via* nitrilation with NaC^{14}N and subsequent hydrolysis. This supposition was substantiated using phthalic anhydride as the blocking agent for the amino group.

Three amino acids have been prepared according to the procedure outlined in relatively good yield. These are 1-C^{14}-labeled glycine, DL-alanine, and DL-leucine.

EXPERIMENTAL

The experimental technique is identical in the case of all three amino acids, and the synthesis of glycine-1-C^{14} will be presented as an example of the method.

Phthaloylglycine. The phthaloyl derivatives of the amino acids were prepared according to the suggestion of Billman and Harting[5] A mixture of finely ground glycine[6] and a 10% excess of phthalic anhydride were fused on an oil bath for 15 min. at 185°. The liquid product, which solidified when cooled, was recrystallized twice from 10% ethanol.

Silver phthaloylglycinate. Five g. of finely powdered phthaloylglycine was suspended in 100 ml. of 10% ethanol and the pH adjusted to 6.5 with 6*N* NaOH. A 25% excess of aqueous silver nitrate was slowly added to the solution with stirring. The white precipitate, silver phthaloylglycinate, was allowed to stand in the dark for 1 hr. It was then filtered under suction. The silver salt was washed three times with water and then twice with acetone-free absolute methanol. Yield: 80–85%.

N-bromomethylphthalimide. The success of the decarboxylation demands that all glassware and reagents be scrupulously dry. The moist silver salt was placed in an oven at 65°. until hard and then powdered. Five g. of the salt was added to a flask fitted with a ground glass joint. The flask was then placed into a borosilicate glass vacuum desiccator containing P_2O_5. The desiccator was evacuated to a pressure of 1 mm. and placed in an oven at 65°. The temperature was slowly increased to 90° over a 2 hr. period. The desiccator was re-evacuated every 4 hr. Drying was continued for a total of 72 hr.

One hundred ml. of anhydrous CCl_4 (distilled and then dried over P_2O_5 for 3 days) was added to the silver phthaloylglycinate and the suspension heated to the boiling point of the solvent on a hot plate. The mixture was allowed to cool for 1 min. at room temperature, and 1.5 equivalents of dry Br_2 (shaken twice with concentrated H_2SO_4) in 5 ml. of anhydrous CCl_4, were added rapidly with shaking. The vigorous evolution of CO_2 was observed immediately. The suspension was shaken for an additional 5 min. and then refluxed gently for 1 hr. The solvent was removed at room

(1) A preliminary report of this investigation has been published.[2] The study was supported in part by a grant from the North Dakota Cancer Society.

(2) Fromm, *Federation Proc.*, **15**, 424 (1956).

(3) Howton, Davis, and Nevenzel, *J. Am. Chem. Soc.*, **76**, 4970 (1954).

(4) Hunsdiecker, Hunsdiecker, and Vogt, U. S. Patent 2,175,181 (1939).

(5) Billman and Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948).

(6) A DL mixture of alanine and leucine was employed in the synthesis of their phthaloyl derivatives.

temperature *in vacuo*, and 35 ml. of a mixture of acetone-free methanol and dioxane (5:2) was added to the residue which contained the *N*-bromomethylphthalimide and some phthaloylglycine. The solution was warmed and then filtered to remove the silver bromide. The pH of the filtrate was adjusted to 6.5 with a saturated solution of NaOH in acetone-free absolute methanol. No attempt was made to isolate the *N*-bromomethylphthalimide.

Labeled N-cyanomethylphthalimide. The labeled nitrile was prepared according to the method of Sakami, *et al.*[7] Sodium cyanide-C^{14}, in 2 ml. of acetone-free absolute methanol, was added to the solution containing the *N*-bromomethylphthalimide. The mixture was shaken and allowed to stand for 6 hr. The nitrile was not isolated.

1-C^{14}-labeled glycine. The solvents containing the labeled *N*-cyanomethylphthalimide were removed *in vacuo* and an acid mixture (22 ml. glacial acetic, 50 ml. 20% HCl) was added to the residue and refluxed for 15 hr. The hydrolysate was cooled in the refrigerator and the insoluble phthalic acid removed by filtration. The filtrate was taken to dryness *in vacuo* at 100° and 25 ml. of concentrated HCl was added. The insoluble sodium chloride was removed and the solution again taken to dryness at 100° *in vacuo*. This procedure was repeated. The residue was finally taken up in a minimal amount of boiling water and 5 volumes of 95% ethanol were added, followed by a small amount of pyridine. The solution was cooled overnight in the refrigerator. The glycine-1-C^{14} was recrystallized twice from an alcohol-water mixture.

Amino acid assay. After recrystallization, the 1-C^{14}-labeled amino acids were chromatographed on paper, located with 0.05% ninhydrin in 1-butanol, and eluted. The activities of the isolated compounds, corrected for self-absorption, were determined in a Tracerlab gas flow counter. The total amount of amino acid was measured by quantitative paper chromatography.[8] Finally, derivatives of the amino acids were prepared and assayed for radioactivity. Within experimental error these derivatives were found to be as radioactive as their amino acid precursors. The results are summarized in Table I.

TABLE I
SYNTHESIS OF 1-C^{14} LABELED AMINO ACIDS

Amino Acid	% Radioactive Yield[a]	Specific Activity $\times 10^4$ counts/minute/mM[b]	Derivative
DL-Alanine	41.3	4.8	Phthaloyl
Glycine	57.5	6.3	Phthaloyl, picrate
DL-Leucine	37.6	2.7	Picrolonate

[a] Calculated on the basis of NaCN-C^{14} used (Activity—2 $\times$ 10^5 counts/minute). [b] Specific activity 39 counts/minute/mM for NaCN-C^{14}.

(7) Sakami, Evans, and Gurin, *J. Am. Chem. Soc.*, **69**, 1110 (1947).

DISCUSSION

The decreased specific activities of the 1-C^{14} amino acids relative to NaCN-C^{14}, in the presence of the higher yield data, suggest the decarboxylation of the silver phthaloyl derivatives is not stoichiometric. Similar findings were reported for organic acids.[9]

While the data presented in Table I suggest that the procedure may be of practical value, the method is limited to those amino acids which form phthaloyl derivatives. It has been reported that tyrosine, tryptophan, taurine, and serine do not form such derivatives, and thus the procedure would not be applicable to these amino acids.[5] Furthermore, phenylalanine might be expected to undergo bromination in the course of the silver salt decarboxylation step.

Acknowledgment. The author wishes to thank Mrs. Miltza Luper and Mr. Robert C. Nordlie for their excellent technical assistance.

GRAND FORKS, N. D.

(8) Awapara, *J. Biol. Chem.*, **178**, 113 (1949).
(9) Stoll and Rouvé, *Helv. Chim. Acta*, **34**, 98 (1951).

[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

1-[(2-Dialkylaminoethoxy)phenyl]-2-amino-1-propanols

ROBERT I. MELTZER AND ARNOLD D. LEWIS

Received December 13, 1956

2-And 4-(2-dimethylaminoethoxy)phenyl- and 2- and 4-(2-diethylaminoethoxy)phenyl-2-amino-1-propanol were synthesized. Derivatives of these compounds, wherein the primary amino group was variously substituted, were also prepared.

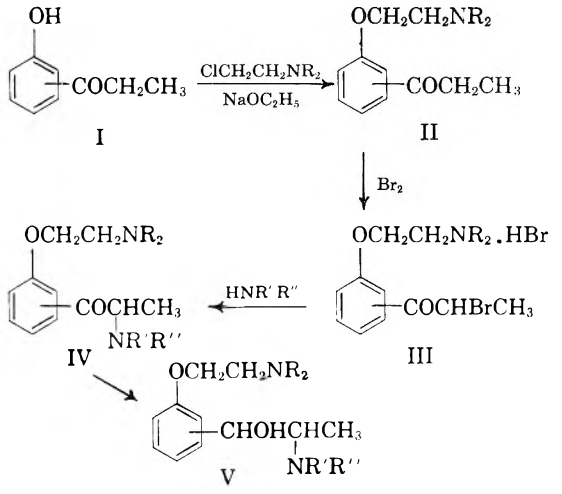
An investigation was undertaken with the object of preparing compounds of the phenethylamine type, having a dialkylaminoalkoxy substituent in the phenyl ring. It was hoped that thereby compounds of pharmacological interest might be attained.

Hundreds of phenethylamine derivatives have been prepared for pharmacological testing. Variations in structure have produced compounds with different sympathomimetic properties of clinical interest. Thus, there have been found among these compounds drugs which act as vasoconstrictors, bronchodilators, central nervous system stimulants, analgetics, and uterine contractors.[1] The relationship between activity and structure has been

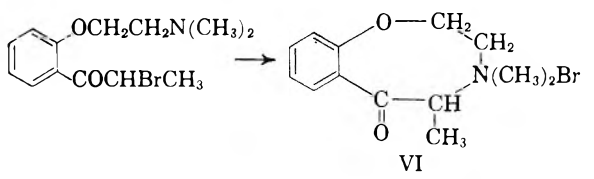
(1) A. Burger, *Medicinal Chemistry*, Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 289–349.

satisfactorily established only for the pressor properties of the phenethylamines. The correlation between structure and other sympathometic properties is comparatively rudimentary. It had been noted that the substitution of an alkoxy group in the 2 position of the phenethylamine skeleton resulted in compounds having good bronchodilator properties and poor pressor effects.[2] With this in mind, we decided to introduce dialkylaminoethoxy groups in the 2 position of the phenethylamine structure in the hope of attaining bronchodilators having other physiological effects at a minimum. We considered it would also be of interest to prepare compounds with the dialkylaminoalkoxy side chain in the 4 position both for the purpose of comparison with the *ortho* compounds and for their possible intrinsic interest. Because of the frequent very appreciable difference in pharmacological properties of dimethylamino and diethylamino groups, both the dimethylaminoethoxy and diethylaminoethoxy compounds were desired.

As starting materials, *o*- and *p*-hydroxypropiophenones (I) were chosen. As their sodium salts, these were etherified in alcoholic solution by the use of dimethylaminoethyl chloride and diethylaminoethyl chloride. The yields of the dialkylaminoalkoxypropiophenones (II) made using the former halide were in general poorer than those made using the second halide.



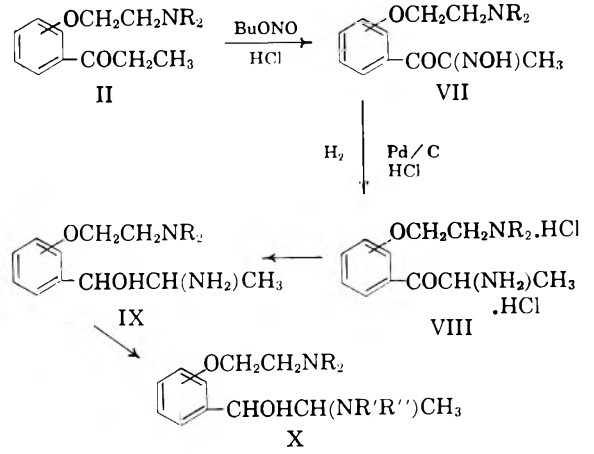
Bromination of *o* - (2 - dimethylaminoethoxy) propiophenone (II, R = methyl) gave the α-bromo product (III, R = methyl) in 50–60% yield. When the base was freed from its hydrobromic acid salt by alkali in the cold, and immediately extracted with ether, there resulted on standing ether-insoluble crystals. This product was water soluble, was not precipitated by alkali, and contained bromine only in the ionic form. Analysis corresponded to that of the compound VI which apparently results by the intramolecular cyclization of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone.



The *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide (III, R = methyl) was allowed to react with large excesses of methylamine, dimethylamine, diethylamine, and morpholine to give the corresponding α-aminoketones (IV). Reduction of the α-dimethylaminoketo and the α-diethylaminoketo compounds gave the corresponding secondary alcohols (V).

All attempted brominations of *p*-(2-dimethylaminoethoxy)propiophenone and *o* and *p*-(2-diethylaminoethoxy)propiophenones gave as the only isolated crystalline compounds the hydrobromides of the starting ketones. Because brominations of this type may be affected by the choice of solvents,[3] the reactions were attempted in chloroform, carbon tetrachloride, water, methanol, ether, and glacial acetic acid, in the presence and the absence of an electric lamp or sunlight, and at low and at elevated temperatures. The failure of these brominations prevented the preparation of the rest of the projected compounds by this method.

A second synthetic route, however, led to the required substances.



Nitrosation of the ketones (II) to isonitrosoketones (VII) was accomplished by the use of butyl nitrite and hydrogen chloride. The amino group in the starting propiophenones (II) made the use of anhydrous ether, the usual solvent, impractical because the amine hydrochloride precipitated completely out of the reaction mixture. By the addition of some alcohol, however, it was possible to get almost quantitative yields. The partially solubilized precipitated aminoketone hydrochloride reacted slowly to give the isonitroso compound which was also insoluble. The end of the reaction could be ascertained by noting the character of the

(2) B. E. Graham and M. H. Kuizenga, *J. Pharmacol. Exptl. Therap.*, **94**, 150 (1948).

(3) A. E. Ardis, R. Baltzly, and W. Schoen, *J. Am. Chem. Soc.*, **68**, 591 (1946).

precipitate. The resulting product in almost quantitative yield was of satisfactory purity for further work.

Reduction of the isonitroso compounds was carried out in two steps.[4] Hydrogenation in alcoholic solution in the presence of palladium on charcoal and of excess hydrogen chloride, gave the diaminoketone dihydrochloride (VIII). This was isolated but not purified, and reduced to the amino alcohol, (IX) in aqueous solution in the presence of fresh catalyst.

Reductive alkylation of the primary amines (IX) using benzaldehyde and hydrogen in the presence of platinum gave the benzylamines (X, R′ = benzyl, R″ = H). In the case of 1-[2-(2-dimethylaminoethoxy)phenyl]-2-amino-1-propanol, the amine was allowed to react with benzaldehyde and the resulting water was removed. Reduction of the reaction product required higher temperature and a longer period, than when the intermediate was not first isolated. This is interesting in view of the findings of other workers that, in the case of ethanolamines, formation of anhydro compounds aided reductive alkylation.[5] The difference may be explicable by assuming that in the presence of water an equilibrium is readily attained among the Schiff's base form, the methylolamine form, and the oxazolidine form, with reduction of all forms taking place. In the absence of water, a slower attainment of equilibrium may result in a greater portion of the reduction taking place *via* less readily reduced forms.

Methylation of the benzyl compounds using formaldehyde and formic acid converted the secondary amines to the tertiary amines (XI, R′ = benzyl, R″ = methyl). The formaldehyde-formic acid method of alkylation was also used to convert the primary amines (IX) obtained by reduction of the isonitroso compounds, to tertiary amines (X, R′ = R″ = methyl). The 1-[2-(2-dimethylaminoethoxy)phenyl]-2-dimethylamino-1-propanol obtained by this procedure was identical with the product obtained *via* the bromoketone intermediate above.

The primary amines (IX) were isopropylated to secondary amines (X, R′ = isopropyl, R″ = H) by reductive alkylation, using acetone and hydrogen in the presence of platinum. Substitution of acetaldehyde for acetone gave a mixture of the monoethylated and diethylated amines which on further ethylation gave the diethylated products (XI, R′ = R″ = ethyl). In the case of the *p*-dimethylaminoethoxy compound, the monoethyl was actually purified. In all other cases the purification of the mixture for attainment of the monoethylated compound was not attempted. The 1-[2-(2-dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol obtained by the reductive diethylation was the same as the product obtained earlier by reduction of *o*-(2-dimethylaminoethoxy)-α-diethylaminopropiophenone.

None of the compounds showed pressor activity. Other sympathomimetic properties are under investigation. Melting points, boiling points, analysis, and recrystallization solvents are reported in Table I.

(4) W. H. Hartung, *J. Am. Chem. Soc.*, **53**, 2248 (1931).

(5) E. M. Hancock and A. C. Cope, *J. Am. Chem. Soc.*, 66, 1738 (1944).

EXPERIMENTAL

(2-Dialkylaminoethoxy)propiophenones (II). The dialkylaminoethyl chloride hydrochloride (1 mole) was placed in a separatory funnel with an equal volume of water and ice and an equal volume of benzene. The aqueous layer was made strongly alkaline with alkali and the benzene layer was separated and dried twice briefly over sodium hydroxide pellets. All this was carried out in the cold.

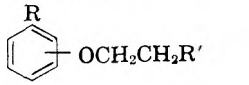
The hydroxypropiophenone (1 mole) was dissolved in 5 times its volume of absolute ethanol in which had previously been dissolved an equivalent of sodium. To this warm solution was added the above benzene solution with stirring. After stirring for at least 1 hr., the solution was kept at reflux for 2 to 4 hr. The solution was filtered and the solvent was removed under vacuum. The residue was taken up in ether and washed with 10% sodium hydroxide to remove unreacted phenol and any quaternary ammonium compounds. From this wash, unreacted phenol could be recovered by acidification. The ether layer was extracted with 6*N* hydrochloric acid and then with concentrated hydrochloric acid. The aqueous extract was made alkaline and extracted with ether. The organic layer was dried over magnesium sulfate and distilled. Yields using dimethylaminoethyl chloride were 30–50% based on starting quantities. As much as 50% of the original starting hydroxypropiophenone could be recovered. Yields using diethylaminoethyl chloride were over 70%.

o-(2-Dimethylaminoethoxy)-α-bromopropiophenone hydrobromide (III, R = methyl). To 241 g. (1.09 mole) of *o*-dimethylaminoethoxypropiophenone in 1200 ml. of methanol was added 174 g. (1.09 mole) of bromine in 1200 ml. of ice cold methanol over a period of 20 min. while keeping the reaction mixture at 10–20° C. and under a 300 watt electric lamp. The reaction mixture was stirred for an additional hour at about 15° and then treated with about 5 ml. of acetone to remove any unreacted bromine. The solvent was then removed on a steam bath until distillation slowed considerably. The residue (about 600 ml.) was cooled and filtered. The product was washed with cold methanol. Further concentration sometimes gave additional material. The yields varied from 30–60% of material melting above 160°. The fully purified product after repeated recrystallization from absolute ethanol melted at 167–168°.

(2-Dialkylaminoethoxy)propiophenone hydrobromides. The free base was dissolved in ether and precipitated with excess hydrogen bromide. The gummy precipitate was recrystallized from absolute ethanol or from 2-propanol.

o-(2-Dimethylaminoethoxy)-α-methylaminopropiophenone hydrochloride (IV.2HCl, R = R′ = methyl, R″ = hydrogen). To 115 g. (3.7 mole) of methylamine in 100 ml. of dry benzene kept at −12 to −17° C. was added 25 g. (0.066 mole) of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide as a fine powder. The reaction mixture was stirred at 2° C. for 4 hr. and then left overnight at room temperature. Most of the excess methylamine was removed under about 100 mm. in a bath at 40° C. The reaction mixture was then extracted with dilute hydrochloric acid. The acid extract was ether washed, made alkaline, and ether extracted. The ether extract was dried over magnesium sulfate and evaporated to dryness to remove the last traces of methyl-

TABLE I



R′	Position	R	M.p.[a] °C.	Solvent for Recryst.	Calculated C	Calculated H	Calculated X	Found C	Found H	Found X
$N(CH_3)_2$	*o*	$COCH_2CH_3$			70.55	8.65		70.59	8.61	
$N(C_2H_5)_2$	*o*	$COCH_2CH_3$	[c]		72.25	9.30		72.38	9.58	
$N(CH_3)_2$	*p*	$COCH_2CH_3$	39–41[d]		70.55	8.65		70.50	8.40	
$N(C_2H_5)_2$	*p*	$COCH_2CH_3$	[e]		72.25	9.30		72.24	9.05	
$N(CH_3)_2$.HBr	*o*	$COCH_2CH_3$	116.5–117.5	A	51.66	6.67	26.43	51.92	6.87	26.33
$N(C_2H_5)_2$.HBr	*o*	$COCH_2CH_3$	100.5–102.5	A	54.55	7.32	24.20	54.66	7.32	24.05
$N(CH_3)_2$.HBr	*p*	$COCH_2CH_3$	151–152	B	51.66	6.67	26.44	51.87	6.85	26.35
$N(C_2H_5)_2$.HBr	*p*	$COCH_2CH_3$	146–147	B	54.55	7.32	24.20	54.69	7.44	24.20
$N(CH_3)_2$.HBr	*o*	$COCHBrCH_3$	167–168	B	40.97	5.02	41.94	41.14	4.91	41.85
$N(CH_3)_2$.HCl	*o*	$COC(NOH)CH_3$	192–192.5	B	54.44	6.68	12.0[f]	54.65	6.81	12.3[f]
$N(C_2H_5)_2$.HCl	*o*	$COC(NOH)CH_3$	166.5–167.5	B	57.22	7.36	11.26	57.23	7.21	11.25
$N(CH_3)_2$.HCl	*p*	$COC(NOH)CH_3$	216–217	B	54.45	6.68	[g]	54.57	6.52	[g]
$N(C_2H_5)_2$.HCl	*p*	$COC(NOH)CH_3$	177–180	B-C	57.22	7.36	11.26	57.29	7.20	11.26
$N(CH_3)_2$.HCl	*o*	$COCH(CH_3)NHCH_3$.HCl	180–181	A-B	52.01	7.48	21.94	52.22	7.71	21.76
$N(CH_3)_2$.HCl	*o*	$COCH(CH_3)N(CH_3)_2$.HCl	193–195	A	53.44	7.77		53.39	7.58	
$N(CH_3)_2$.HBr	*o*	$COCH(CH_3)N(C_2H_5)_2$.HBr	173–175	A	44.94	6.66	35.18	44.81	6.46	35.08
$N(CH_3)_2$.HBr	*o*	$COCH(CH_3)\overline{NCH_2CH_2OCH_2CH_2}$.HBr	207.5–209	B	43.60	6.03	34.14	43.53	5.85	33.96
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)NH_2$.HCl	246–247.5[h]	C	50.16	7.77	22.78	49.93	7.93	22.50
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)NH_2$.HCl	197.5–198	B	53.09	8.32	20.90	52.96	8.12	20.78
$N(CH_3)_2$.HBr	*p*	$CHOHCH(CH_3)NH_2$.HBr	109–112[i]	A-B	39.01	6.04	39.94	38.81	6.20	39.61
$N(C_2H_5)_2$	*p*	$CHOHCH(CH_3)NH_2$	70–71	D	67.63	9.84	[j]	67.82	9.82	[j]
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	216–217	B	53.09	8.32	20.90	52.86	7.83	20.52
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	195–197.5	E-F	55.58	8.78	19.30	55.39	8.49	19.28
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	255.5–257	B-C	53.09	8.32	20.90	52.82	8.04	20.78
$N(C_2H_5)_2$.HCl	*p*	$CHOHCH(CH_3)N(CH_3)_2$.HCl	229.5–232	B-G	55.58	8.78	19.30	55.77	8.60	19.11
$N(CH_3)_2$.HBr	*o*	$CHOHCH(CH_3)N(C_2H_5)_2$.HBr	216.5–217.5	B-G	44.75	7.07	35.03	45.01	7.10	35.11
$N(C_2H_5)_2$.HBr	*o*	$CHOHCH(CH_3)N(C_2H_5)_2$.HBr	183.5–186	B	47.11	7.49	33.00	47.32	7.21	33.05
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)N(C_2H_5)_2$.HCl	210–212	A-B	55.58	8.78	19.30	55.35	9.03	19.05
$N(C_2H_5)_2$.HBr	*p*	$CHOHCH(CH_3)N(C_2H_5)_2$.HBr	214–215	B	47.11	7.49	33.00	47.36	7.71	33.08
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HCl.$3H_2O$	111–113	E-H	52.74	7.97	15.57[k]	52.79	7.89	15.69[k]
$N(C_2H_5)_2$.HBr	*o*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HBr	198–199	B	50.97	6.61	30.84	50.91	6.39	30.56
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HCl	233–235	B	59.84	7.53	17.67	59.82	7.27	17.83
$N(C_2H_5)_2$.HCl	*p*	$CHOHCH(CH_3)NHCH_2C_6H_5$.HCl	225.5–227	B-C	61.53	7.98	16.51	61.34	7.64	16.25
$N(CH_3)_2$.HCl	*o*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HCl	183–184[l]	A	54.38	8.56	20.07	54.39	8.68	19.76
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HCl	210.5–212	A-B	56.68	8.99	18.59	56.45	8.71	18.40
$N(CH_3)_2$.HBr	*p*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HBr	175.5–176.5[m]	A-B	43.45	6.84	36.1	43.42	6.62	36.1
$N(C_2H_5)_2$.HBr	*p*	$CHOHCH(CH_3)NHCH(CH_3)_2$.HBr	118–121	A	45.97	7.29	33.99	45.78	7.28	34.10
$N(C_2H_5)_2$.HCl	*o*	$CHOHCH(CH_3)N(CH_3)CH_2C_6H_5$.HCl	202–204	A-G	62.29	8.18	15.99	62.17	8.41	15.66
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)N(CH_3)CH_2C_6H_5$.HCl	196.5–198	A	60.71	7.77	17.01	60.45	7.66	17.04
$N(CH_3)_2$.HCl	*p*	$CHOHCH(CH_3)NHC_2H_5$.HCl	243.5–244.5	B-C	53.09	8.32	20.90	52.28	8.32	20.72

[a] Temperatures are uncorrected. Melting points were taken on a Fisher-Johns melting point block. [b] B.p. 107–9° (0.06 mm.), n_D^{25} 1.5182. [c] B.p. 126–8° (0.5 mm), n_D^{25} 1.5124. [d] B.p. 117° (0.15 mm.), n_D^{25} 1.5303. [e] B.p. 137° (0.4 mm.), n_D^{27} 1.5221. [f] N: calcd., 9.78; found, 9.92. [g] N: calcd., 9.78; found. 9.69. [h] Free base from ether, m.p. 65–66°. [i] Free base from benzene, m.p. 97.5–98°. [j] N: calcd., 10.52; found, 10.46. [k] N: calcd. 6.15, found: 6.15, A-isopropanol, B-ethanol (abs.), C-methanol, D-Skellysolve B, E-1-butanol, F-ethyl acetate, G-ether, H-water. [l] Free base from Skellysolve B, m.p. 72.5–73.5°. [m] Free base from benzene, m.p. 87–87.5°.

amine. The residue was taken up in ether and treated with dry hydrogen chloride to complete the precipitation. The gummy residue was crystallized from 2-propanol and purified from 1:1 2-propanol–ethanol. The yield of pure product was 1.7 g. (7%).

o-(2-Dimethylaminoethoxy)-α-N-morpholinopropiophenone hydrobromide (*IV.2HBr, R = methyl, NR′R″ = morpholine*). To 800 g. (9.2 moles) of dried, distilled morpholine was added with stirring and keeping the temperature below 35°, 100 g., (0.26 mole) of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide. The reaction was stirred for 6 hr., heated to 90° and stirred overnight while allowing the solution to cool to room temperature. Addition of a liter of ether precipitated the morpholine hydrobromide which was removed by filtration. The remaining morpholine was removed by distillation under 1 mm. from a bath at 50° C. The residue was taken up in ether, washed with water, dried over magnesium sulfate, and treated with ethereal hydrogen bromide to complete precipitation. The yield of crystalline material melting at 204–5° was 60% of theory. Recrystallization from ethanol raised the melting point to 207.5–209°.

o-(2-Dimethylaminoethoxy)-α-diethylaminopropiophenone hydrobromide (*IV.2HBr, R = methyl, NR′R″ = N*(C_2H_5)$_2$. To 475 g. (15 moles) of diethylamine was added with stirring 76.2 g. (0.2 mole) of finely powdered *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide. The temperature of the reaction mixture rose from 25 to 28°. Stirring was continued overnight. The reaction mixture was then filtered to remove the diethylamine hydrobromide and the filtrate distilled to recover the excess diethylamine. Last traces of diethylamine were removed on a water bath (45° C) at 1 mm. pressure. The residue was taken up in 200 ml. anhydrous ether and gaseous HBr added to the Congo Red endpoint. The hydrobromide precipitated as a sticky hygroscopic solid. This was then recrystallized to give a 33% yield of pure product.

o-(2-Dimethylaminoethoxy)-α-dimethylaminopropiophenone hydrochloride (*IV.2HCl, R = R′ = R″ = methyl*). To a solution of 60 g. (1.33 moles) of dry dimethylamine in 300 ml. of absolute ethanol kept at below 10° C. was added a hot solution of 90 g. (0.24 mole) of *o*-dimethylaminoethoxy-α-bromopropiophenone hydrobromide in 900 ml. of absolute ethanol. Stirring was continued until room temperature was attained and for an additional 2 hr. The alcohol was removed by distillation. The residue was taken up in 200 ml. of 5*N* ammonium hydroxide and 300 ml. of ether. The ether layer, after drying over magnesium sulfate, was distilled. Redistillation gave a fraction boiling at 127–130°/0.6 mm. This was dissolved in 2-propanol and treated with dry hydrogen chloride. The precipitate was purified by recrystallization from 2-propanol.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol dihydrobromide (*V.2HBr, R = methyl, R′ = R″ = ethyl*). This was obtained by reduction of *o*-(2-dimethylaminoethoxy)-α-diethylaminopropiophenone dihydrobromide in water solution at 100° and at 1000 lbs. pressure in the presence of 10% palladium on charcoal. Filtration and evaporation to dryness gave a white solid which was purified by recrystallization from an ethanol-ether mixture.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-dimethylamino-1-propanol dihydrochloride. (*V.2HCl, R = R′ = R″ = methyl*). This was prepared by reduction of *o*-(2-dimethylaminoethoxy)-α-dimethylaminopropiophenone dihydrochloride in aqueous solution at 100° and at 1000 lbs. pressure in the presence of 10% palladium on charcoal. Filtration and evaporation to dryness gave an oil which was crystallized from ethanol.

Cyclization of o-(2-Dimethylaminoethoxy)-α-bromopropiophenone. To a solution of 76 g. of *o*-(2-dimethylaminoethoxy)-α-bromopropiophenone hydrobromide in 500 ml. of water and ice, overlayered by 4 l. of ether, was added 100 ml. of 20% sodium hydroxide while stirring vigorously. The layers were separated as quickly as possible. The aqueous layer was washed once with ether. The combined ether layers were dried over magnesium sulfate for a few minutes and gravity filtered. The whole operation took about 20 min. The clear filtrate became cloudy in less than 5 min. After 5 days, filtration yielded 37.5 g. of crystals melting over 200°. Recrystallization from propanol-methanol mixture in the presence of Darco gave crystals m.p. 202–204°. This material is soluble in water and in alkali and analysis agreed with that for 1,8-dimethyl-5,6-benzo-1,3-azoxycyclooctan-7-one methobromide.

Anal. Calcd. for $C_{13}H_{18}BrO_2N$: C, 52.01; H, 6.04; N, 4.67; Br, 26.6. Found: C, 52.05; H, 6.08; N, 4.66; Br, 26.7.

o-Dialkylaminoethoxy-α-isonitrosopropiophenone hydrochloride (*VII*). Into a solution of 0.6 mole of (2-dialkylaminoethoxy)propiophenone in 550 ml. absolute ethanol-ether (2:5) solution was passed 0.8 mole of hydrogen chloride while stirring vigorously and cooling with an ice bath. To the resulting thick semi-solid mixture was added with stirring, 0.9 mole of butyl nitrite at such a rate as to cause and maintain very gentle refluxing. Stirring was continued at room temperature for about 2.5 hr. after addition was completed. The appearance of the precipitate changed during this time to a heavier and more granular looking material. The reaction mixture was filtered, washed with ethanol-ether and dried. The yield of product thus obtained was almost quantitative, of sharp melting point and satisfactory for reduction.

1-[(2-Dialkylaminoethoxy)phenyl]-2-amino-1-propanol (*IX*). The reduction of 0.38 mole of isonitroso compound as its hydrochloride was carried out in 1 liter of absolute alcohol containing 1.15 moles of additional hydrogen chloride in the presence of 11 g. of 10% palladium on charcoal and under about 1000 lbs. hydrogen pressure. After the theoretical hydrogen uptake for reduction of the isonitroso was completed, the reaction mixture was evaporated to dryness. The catalyst may or may not have been removed first. The residue was taken up in water to make a liter of solution. Another 11 g. of catalyst was added and reduction was continued. After the theoretical hydrogen uptake for the reduction of carbonyl, the solution was filtered and evaporated to dryness. The residue was recrystallized from the appropriate solvent.

In the case of the *p*-dimethylaminoethoxy isomer it was sometimes necessary to heat the reaction mixture to about 100° during the second reduction in order to expedite it. Instead of evaporating the aqueous reduction mixture to dryness, it was concentrated, made alkaline with 50% sodium hydroxide, and extracted with benzene. Concentration of the benzene gave the crystalline free base. Recrystallization from benzene gave a melting point of 96–97.8°. The base in ether solution was converted to its hydrobromide using gaseous hydrogen bromide.

In the case of the *o*-diethylaminoethoxy isomer it was advisable to heat during both reductions. On concentration of the aqueous reduction, the concentrated solution was made alkaline with 50% sodium hydroxide and extracted with ether. Hydrogen chloride in ether converted the base to its salt.

In the case of the *p*-diethylaminoethoxy isomer the aqueous reduction mixture was made alkaline with 50% sodium hydroxide and extracted with benzene. The dried benzene extract on concentration gave the crystalline base. We were unable to get a non-hygroscopic salt.

The over-all yields for the reductions were 40–70%.

1-[(2-Dialkylaminoethoxy)phenyl]-2-benzylamino-1-propanol. (*X, R′ = benzyl, R″ = hydrogen*). To the suspension obtained by reducing 200 mg. of platinum oxide in 25 ml. of absolute ethanol was added 10 mmoles of the primary amine and 11 mmoles of freshly distilled benzaldehyde in 50 ml. of absolute ethanol. After shaking with hydrogen until the theoretical amount of hydrogen was taken up, the reaction mixture was filtered. An excess of concentrated hydrochloric or hydrobromic acid was added and crystalli-

zation was induced by seeding, scratching, and/or concentration.

In the case of the *o*-dimethylaminoethoxy isomer, the ethanol mother liquor was evaporated and replaced by 1-butanol before addition of the concentrated hydrochloric acid. The reduction in the case of this isomer took about 3 hr. at room temperature for 20 mmoles. The following variation increased the temperature and time required for the reaction. The amine and benzaldehyde were mixed in 50 ml. of benzene. After 2 hr., the water which separated was removed by magnesium sulfate and the benzene was removed under vacuum. Absolute ethanol was added and also removed under vacuum. The ethanol was replaced and the solution added to the reduced catalyst as above. At room temperature there was practically no hydrogen uptake at atmospheric pressure or at 50 lbs. pressure. At about 60–75°, several hours were required.

1-[(2-Dialkylaminoethoxy)phenyl]-2-benzylmethylamino-1-propanol (*X*, *R′* = *benzyl*, *R″* = *methyl*). In a manner similar to the methylation of the primary amine to give the dimethylamine, the benzylamine was methylated using formic acid and formaldehyde.

1-[(2-Dialkylaminoethoxy)phenyl]-2-dimethylamino-1-propanol (*X*, *R′* = *R″* = *methyl*). A solution of 20 mmoles of the primary amine base, 200 mmoles of 98–100% formic acid and 250 mmoles of formaldehyde as its 40% aqueous solution, was kept in a bath at 120° for about 3 hr. and at 145° for about the same length of time. To the reaction mixture was added 6 ml. of concentrated hydrochloric acid. The residue obtained on evaporation to dryness on a steam bath under vacuum was taken up in concentrated hydrochloric acid and again evaporated to dryness. The residue was now crystallized and recrystallized from the appropriate solvent.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-dimethylamino-1-propanol (*V or X*, *R* = *R′* = *R″* = *methyl*) was also obtained, as described above, *via o*-(2-dimethylaminoethoxyphenyl)-α-bromopropiophenone hydrobromide.

1-[(2-Dialkylaminoethoxy)phenyl]-2-isopropylamino-1-propanol (*X*, *R′* = *isopropyl*, *R″* = *hydrogen*). To a suspension obtained by reducing 200 mg. of platinum oxide in 25 ml. of alcohol was added a day-old solution of 20 mmoles of the primary amine and 25 mmoles of acetone. After uptake of the theoretical quantity of hydrogen, the reaction mixture was concentrated to dryness. In all but the *p*-diethylaminoethoxy isomer (an oil), solid free bases were obtained as residues. The residues were dissolved in the solvent from which the salt was to be recrystallized and the appropriate hydrogen halide was added.

1-[(2-Dialkylaminoethoxy)phenyl]-2-diethylamino-1-propanol (*X*, *R′* = *R″* = *ethyl*). To a solution of 20 mmoles of the primary amine in 50 ml. of absolute ethanol was added 20 mg. of platinum oxide and 50 mmoles of freshly distilled acetaldehyde while keeping the reaction flask in an ice bath. Hydrogen was introduced with shaking at atmospheric pressure and temperature until no further hydrogen uptake occurred. An additional 50 mmoles of acetaldehyde was added and reduction again continued until cessation of hydrogen uptake. The catalyst was removed by filtration. The residue obtained on evaporation of the filtrate, was taken up in 2-propanol and made acid to Congo Red with hydrogen bromide or hydrogen chloride. The resulting solid was recrystallized.

1-[2-(2-Dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol (*V or X*, *R* = *methyl*, *R′* = *R″* = *ethyl*) was prepared in this way, and also as described above *via o*(2-dimethylaminoethoxyphenyl)-α-bromopropiophenone hydrobromide.

1[4-(2-Diethylaminoethoxy)phenyl]-2-ethylamino-1-propanol dihydrochloride (*X.2HCl*, *R* = *methyl*, *R′* = *ethyl*, *R″* = *hydrogen*). This was prepared in the same way that 1-[4-(2-dimethylaminoethoxy)phenyl]-2-diethylamino-1-propanol was prepared except that the second reduction in the presence of acetaldehyde was omitted. Repeated recrystallization from ethanol-methanol solvent gave 25–30% yield of product which showed no primary amine by Van Slyke analysis and analyzed as expected for the monoethylated product.

MORRIS PLAINS, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Beckmann Rearrangement of Some Cyclic Sulfone Ketoximes[1]

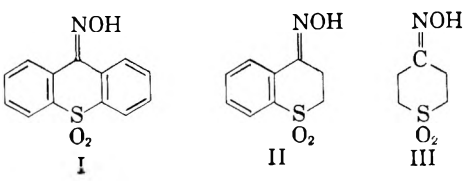
WILLIAM E. TRUCE AND JOHN A. SIMMS[2]

Received December 17, 1956

The ease of rearrangement of thiaxanthone 5,5-dioxide oxime (I), 4-thiachromanone 1,1-dioxide oxime (II), and tetrahydro-1,4-thiapyrone 1,1-dioxide oxime (III) was found to be III ≫ II ≧ I. The rearrangement product of I was characterized by independent synthesis.

It has been show that some heterocyclic ketoximes undergo the Beckmann rearrangement to give the expected lactams.[3–5] However, all of the ketoximes previously examined had the ketoxime function separated from the hetero atom by saturated carbon atoms. It was felt that an appreciable change in reactivity might result if the hetero atom was conjugated with the oxime group.

Therefore, the three cyclic sulfone ketoximes, thiaxanthone 5,5-dioxane oxime (I), 4-thiachromane 1,1-dioxide oxime (II), and tetrahydro-1,4-thiapyrone 1,1-dioxide oxime (III), were prepared and the conditions necessary for their rearrangement were determined.



(1) Taken from Mr. Simms' Ph.D. Thesis, Purdue University, 1956.

(2) Dow Chemical Company Fellow, 1954–1955.

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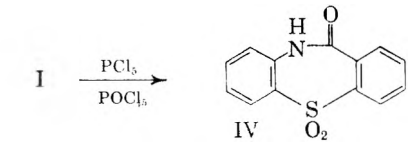
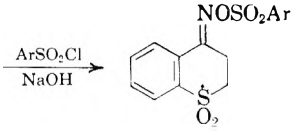
Oxime I was synthesized from the known ketone, thiaxanthone 5,5-dioxane.[6-8] A 70% yield of the normal rearrangement product, the lactam of 2-(2′-aminobenzenesulfonyl)benzoic acid (IV), was isolated after refluxing a mixture of I with phosphorus pentachloride and phosphorus oxychloride for 48 hr.



Compound IV is easily hydrolyzed, but the 2-(2′-aminobenzenesulfonyl)benzoic acid (V) obtained re-cyclized upon drying at 100°. The independently synthesized[9] V behaved similarly, and it appears that the melting point observed is for the lactam rather than for the free amino acid.

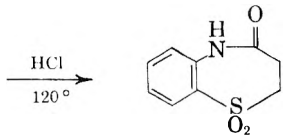
4-Thiachromanone 1,1-dioxide[10] was prepared from thiophenol and β-chloropropionic acid. Its oxime (II) forms more easily than the oxime of thiaxanthrone 5,5-dioxide. 4-Thiachromanone 1,1-dioxide oxime (II) did not rearrange when it was treated with a number of acid catalysts. Treatment of the oxime in refluxing phosphorus oxychloride with phosphorus pentachloride resulted in tar formation; no reaction was observed with phosphorus pentachloride in diethyl ether. The oxime was isolated unrearranged from concentrated sulfuric acid, although it was hydrolyzed to 4-thiachromanone 1,1-dioxide by 85% sulfuric acid. Polyphosphoric acid caused extensive tar formation.

4-Thiachromanone 1,1-dioxide oxime (II) formed stable N-arylsulfonates in good yield.



The benzenesulfonate (VI) was recovered quantitatively after 6 hr. heating at 100° in methanol solution. Under similar conditions, benzophenone oxime *N*-benzene sulfonate is completely rearranged in 10 min.[11]

When VI was heated with polyphosphoric acid, or concentrated hydrochloric acid, only intractable oils were obtained. However, it was possible to rearrange the *o*-nitrobenzenesulfonate (VII) with concentrated hydrochloric acid. The lactam of



2-(2′-aminobenzenesulfonyl)propionic acid[12] (VIII) was produced in 43% yield. The configuration assigned to the 4-thiachromanone 1,1-dioxide oxime (II) is consistent with the structure of the rearrangement product, using the concept of *trans* rearrangement.[11, 11a]

Tetrahydro-1,4-thiapyrone 1,1-dioxide oxime[12b] (III) was prepared in 90% yield from the corresponding ketone.[13] When it was heated for 3 min. with 85% sulfuric acid, all the oxime dissolved without any discoloration of the solution. Chloroform extraction after neutralization with potasssium hydroxide did not separate the product. The solution was then evaporated to dryness and the residue extracted with methanol in a soxhlet extractor. An organic salt containing potassium but no sulfate was thus separated. Although this material was not further characterized, it is probably potassium 2-(2′-aminoethylsulfonyl)propionate. Tetrahydro-1,4-thiapyrone-1,1-dioxide oxime (III) had been rearranged with polyphosphoric acid[12b] but the product was not isolated.

Electron withdrawing groups introduced into the acetophenone portion of substituted acetophenone oximes[14] or acetophenone oxime picryl ethers[15] caused the Beckmann rearrangement to proceed much more slowly than in the unsubstituted compounds.

A similar deactivating effect is observed in the rearrangement of thiaxanthone 5,5-dioxide oxime (I). This compound was even less reactive than anthraquinone monoxime[16,17] (45 hr. *vs.* 5 hr. under the same reaction conditions for complete rearrangement).

A direct comparison of the relative rates at which thiaxanthone 5,5-dioxide oxime (I) and 4-thiachromanone 1,1-dioxide oxime (II) rearrange could not be made because of the decomposition of the latter oxime when it was refluxed with phosphorus pentachloride in phosphorus oxychloride in phosphorus oxychloride solution. It can be estimated from the vigor of the conditions necessary to obtain rearrangement of the corresponding *o*-nitrobenzenesulfonate that 4-thiachromanone 1,1-dioxide oxime is approximately equal to thiaxan-

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thione 5,5-dioxide oxime in resistance to rearrangement.

Tetrahydro-1,4-thiapyrone-1,1-dioxide oxime (III) rearranges very readily when treated with 85% sulfuric acid. 4-Thiachromanone 1,1-dioxide oxime (II) is isolated in good yield after heating for 1 hr. with concentrated sulfuric acid, thus making the ease of rearrangement in this series: tetrahydro-1,4-thiapyrine-1,1-dioxide oxime (III)$\gg$4-thiachromanone-1,1-dioxide oxime (II) $\cong$thiaxanthone 5,5-dioxide oxime (I).

EXPERIMENTAL[18]

Thiaxanthone 5,5-dioxide Oxime (I). Thiaxanthone was prepared from benzene and thiosalicyclic acid in 68% yield as a light yellow solid (m.p. 213–214°; lit.[7] 209°) by the method of Davis and Smiles[7] using the more specific directions given by Gomberg and Britton.[8] It was oxidized with a solution of hydrogen peroxide in acetic acid according to Ullmann.[6] A quantitative yield of thiaxanthone 5,5-dioxide, m.p. 187–188.5° (lit.[6] 187°), was obtained.

The oxime was produced when a mixture of 10 g. (0.041 mole) of thiaxanthone 5,5-dioxide, 16 g. (0.24 mole) of hydroxylamine hydrochloride, and 30 ml. (0.37 mole) of pyridine in 150 ml. of ethyl alcohol was refluxed for 23 hr. The clear solution that resulted was cooled and poured into ice water. The precipitate that formed was filtered and washed well with hot water to remove any occluded pyridine hydrochloride. The dried oxime, 9.6 g. (92%), m.p. 209–211°, was recrystallized from absolute ethanol in two fractions: (1) 6.5 g., m.p. 213–214°; (2) 1.6 g., 213–213.5°.

Anal. Calcd. for $C_{13}H_9O_3NS$: C, 60.23; H, 3.50; N, 5.40. Found: C, 60.32; H, 3.82; N, 5.27.

Shorter reaction times produced a mixture containing unreacted thiaxanthone 5,5-dioxide.

Beckmann rearrangement of thiaxanthone 5,5-dioxide oxime. A solution of 10.2 g (0.048 mole) of phosphorus pentachloride in 75 ml. of phosphorus oxychloride was rapidly added to a solution of 9 g. (0.034 mole) of thiaxanthone 5,5-dioxide oxime in 125 ml. of phosphorus oxychloride. After the clear yellow mixture had been refluxed for 48 hrs, 100 ml. of solvent was removed and the cooled residue was poured into ice water with vigorous stirring. The yellow oil which precipitated decomposed to give a yellow white solid. Extraction of the filtrate with ether yielded some more solid. The combined solids were heated for 1 hr. with 300 ml. of 50% sulfuric acid to complete the decomposition of the rearrangement complex The sulfuric acid mixture was cooled and the product (8.1 g.; m.p. 200–275°) recovered by filtration. It was heated for 1.5 hr. with 300 ml. of 7% sodium hydroxide. The alkali-insoluble residue (0.9 g.; m.p. 187–189°) was identified as thiaxanthone 5,5-dioxide. The filtrate was acidified and the precipitate (6.3 g., m.p. 284–294°) that formed was separated by filtration and dried. It was recrystallized from a mixture of ethanol and acetic acid in three fractions: (1) 1.1 g., m.p. 291–292.5°; (2) 1.5 g., 289–291°; (3) 1.7 g., 289.5–290°. A mixture of fraction 1 and 2-(2′-aminobenzenesulfonyl)benzoic acid (m.p. 287–288°) melted sharply at 289°. It is probable that this is the melting point of the corresponding lactam. An analytical sample cyclized when it was dried under vacuum in an Abderhalden apparatus at 100° for 15 hr.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 56.31; H, 4.00; N, 6.05. Calcd. for $C_{13}H_9NO_3$: C, 60.32; H, 3.82; N, 5.27. Found: C, 59.90; H, 4.08; N, 5.42.

The yield of rearrangement product dropped when a reflux time of 16 hr. was used. More thiaxanthone 5,5-dioxide was also isolated.

2-(2′-Aminobenzenesulfonyl)benzoic acid.[9] This compound was prepared in low yield by a three-step synthesis starting with *o*-thiosalicylic acid and *o*-nitrochlorobenzene.

o-Thiosalicylic acid (50 g., 0.325 mole) was added to a solution prepared by dissolving 15.0 g. (0.65 mole) of sodium in 300 ml. of absolute ethanol. A solution of 51 g. (0.324 mole) of *o*-nitrochlorobenzene in 300 ml. of absolute ethanol was then added and the mixture refluxed, with stirring, for 4 hr. The solid that formed was collected, dissolved in water, and filtered. When the filtrate was acidified with hydrochloric acid, a dark, tarry solid precipitated. It was precipitated from alcoholic solution with water and then recrystallized from chloroform to produce 28.8 g. (33%) of 2-carboxyphenyl 2′-nitrophenyl sulfide as a brown solid, m.p. 166–169°.

The above sulfide (24 g., 0.0875 mole) was dissolved in 200 ml. of glacial acetic acid and 29 ml. (0.252 mole) of 30% hydrogen peroxide was added at a rate such that gentle reflux was maintained. After an additional three-hour reflux period, the solution was concentrated to yield 2-(2′-nitrobenzenesulfonyl)benzoic acid, wt. 21.5 g. (85%), m.p. 198–200°.

The 2-(2′-nitrobenzenesulfonyl)benzoic acid (10 g., 0.025 mole) was suspended in 200 ml. of concentrated hydrochloric acid and the mixture was heated to reflux. Tin (1.7 g) was carefully added so as to minimize the initial vigorous reaction. The remaining tin (22 g. a total of 0.206 mole) was added in small portions and the mixture heated on the steam cone for 3 hr. The product (8.9 g., m.p. 284–288°) precipitated from the cooled reaction mixture. It was recrystallized from a mixture of ethanol and acetic acid in three fractions: (1) 4.7 g., m.p. 287–289°; (2) 1.3 g., m.p. 285–287°; (3) 0.7 g., m.p. 280–285°. A sample for analysis (m.p. 287–288°) was recrystallized three times from the same solvent mixture and then dried in a Abderhalden apparatus at 100° for 15 hr. This amino acid evidently cyclized during the drying operation to form the corresponding lactam.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Calcd. for $C_{13}H_9NO_3S$: C, 60.32; H, 3.82; N, 5.27. Found: C, 59.46; H, 3.87; N, 5.30.

4-Thiachromanone 1,1-dioxide. This sulfone was prepared from β-chloropropionic acid and thiophenol *via* β-phenylmercatopropionic acid (83% yield) and thiachromanone (68% yield) by the method of Arndt.[10] Oxidation with hydrogen peroxide in acetic acid produced 4-thiachromanone sulfone (m.p. 128–129.5°; lit.[10] 131–132°) in 64% yield.

4-Thiachromanone sulfone oxime (II). A solution of 20 g. (0.0102 mole) of 4-thiachromanone sulfone, 42.8 g. (0.612 mole) of hydroxylamine hydrochloride, and 74 ml. (0.918 mole) of pyridine in 500 ml. of absolute ethanol was refluxed for 45 hr. The solution was concentrated to 300 ml. and then poured into ice water. The precipitate was washed with three 100 ml. portions of hot water leaving a residue of 19.0 g. (m.p. 189–192°) of grey white solid. Ether extraction of the filterate and wash water yielded, after recrystallization from water, an additional 4.5 g. (m.p. 187–189°) of oxime. Recrystallization of the combined fractions from water gave 19.1 g. (82%) of oxime, m.p. 191–192°. The analytical sample melted at 193.5–194.5° after three more recrystallizations from water.

Anal. Calcd. for $C_9H_9O_3NS$: C, 51.17; H, 4.29; N, 6.63. Found: C, 51.12; H, 4.31; N, 6.95.

Attempted Beckmann rearrangement of 4-thiachromanone 1,1-dioxide oxime. None of the expected rearrangement product, the lactam of 2-(2′-aminobenzenesulfonyl)propionic acid, was isolated in any of the experiments outlined in Table 1. The catalysts caused tar formation, or hydrolysis to thiachromanone 1,1-dioxide as the principle reactions observed. In a number of cases the oxime was recovered. It is very resistant to hydrolysis or rearrangement when heated with concentrated sulfuric acid. Less concentrated sulfuric acid (85%) causes rapid hydrolysis to 4-thiachromanone 1,1-dioxide.

4-Thiachromanone 1,1-dioxide oxime N-benzenesulfonate (VI). 4-Thiachromanone 1,1-dioxide oxime (6.33 g., 0.03

(18) All melting points are uncorrected.

TABLE 1

Expt.[a]	Catalyst	Solvent	Reaction Time and Temperature	Products Isolated
1	PCl_5	$POCl_3$	4 hrs. at 25° 21 hrs. at reflux	Tar and recovered oxime
2	PCl_5	Ethyl ether	12 hrs at 25°	70% recovery of oxime
3	PCl_5	Ethyl ether	6 days at reflux	Low yield of thiachromanone 1,1-dioxide
4	PCl_5	$CHCl_3$	14 hrs. at 25°, 24 hrs. at reflux	Mixture of oxime and thiachromanone 1,1-dioxide
5	85% H_2SO_4	85% H_2SO_4	3 min. on steam plate	65% Yield of thiachromanone 1,1-dioxide
6	93% H_2SO_4	93% H_2SO_4	1 hr. on steam plate	83% Recovery of oxime
7	Polyphosphoric acid	Polyphosphoric acid	6 min. at 115°	Tar and recovered oxime

[a] All these experiments were run on 2 g. samples of the oxime.

mole) was mixed with 225 ml. of water and 5.55 g. (0.0315 mole) of benzenesulfonylchloride was added. After the rapid addition of 33 ml. of 1*N* sodium hydroxide solution, the mixture was stirred for 19 hr. at room temperature and then refluxed for 1 hr. Dilution with water and cooling caused the precipitation of 6.05 g. (m.p. 144–147°), 57% of light brown solid. The pure benzenesulfonate, obtained by recrystallization from methanol and then from a mixture of ether and chloroform, was a white crystalline solid (m.p. 150.5–151°).

Anal. Calcd. for $C_{15}H_{13}NS_2O_5$: C, 51.28; H, 3.72; N, 3.98. Found: C, 51.04; H, 3.90; N. 3.85.

This oxime sulfonate did not rearrange when it was heated with polyphosphoric acid for 0.5 hr. at 140°. The product contained 20% of the starting oxime sulfonate, as well as a considerable quantity of tar. The oxime sulfonate was recovered quantitatively after 6 hr. heating at 100° in methanol solution in a sealed tube. Concentrated hydrochloric chloric acid, with heating at 120° for 3 hr., produced only tar.

Thiachromanone 1,1-dioxide oxime o-nitrobenzenesulfonate (VII). Using the same procedure given above, 2.10 g. (0.01 mole) of thiachromanone sulfone oxime and 2.33 g. (0.01 mole) of *o*-nitrobenzenesulfonyl chloride[19] yielded 3.52 g. (m.p. 179–180°) of the corresponding *o*-nitrobenzenesulfonate. After four recrystallizations from a mixture of dioxane and water, this material melted with decomposition at 182.5°. The analytical results indicate that it was still rather impure.

Anal. Calcd. for $C_{15}H_{12}O_7N_2S_2$: C, 45.45; H, 3.03; N, 7.08. Found: C, 43.92; H, 2.50; N. 5.62.

Rearrangement of 4-thiachromanone 1,1-dioxide o-nitrobenzenesulfonate. The oxime sulfonate (0.90 g., m.p. 180–181°) was heated with 40 ml. of concentrated hydrochloric acid in a sealed tube at 120° for 12 hr. The resulting dark brown mixture was poured into ice water and the precipitate (0.10 g., m.p. 169–179°) of unrearranged sulfonate filtered off. The oil that was obtained by concentrating the filtrate under an air jet was dissolved in methanol and ether was added. A dark brown crystalline material (wt. 0.21 g., m.p. 234–240°, 43% yield) precipitated. The 2-(2′-aminobenzenesulfonyl)propionic acid lactam was purified by another precipitation from ethanol solution with ether; m.p. 243–244° (lit.[12] m.p. 246–247°).

Tetrahydro-1,4-thiapyrone-1,1-dioxide. Tetrahydro-1,4-thiapyrone (m.p. 60–63°; lit.[19] m.p. 65–66°) was prepared in 10% yield by the Dieckmann condensation of methyl β-thiodipropionate.[20] It was oxidized to the corresponding sulfone (m.p. 171°, lit.[13] 170°) in 90% yield with 30% hydrogen peroxide in glacial acetic acid.

Tetrahydro-1,4-thiapyrone 1,1-dioxide oxime[12] (III). A mixture of 3.6 g. (0.24 mole) of tetrahydro-1,4-thiapyrone 1,1-dioxide, 2.1 g. (0.29 mole) of hydroxylamine and 2.6 g., (0.024 mole) of sodium carbonate in 150 ml. of water was heated to reflux and then was allowed to stand for 11 hr. The reaction mixture was evaporated to dryness and the residual solid extracted with chloroform in a Soxhlet extractor for 72 hr. Evaporation of the extract yielded 1.57 g. (m.p. 197–201°; lit.[12] 197–198°) of the oxime.

Rearrangement of the oxime of tetrahydro-1,4-thiapyrone 1,1-dioxide oxime. The *Organic Synthesis* procedure[21] for cyclohexanone oxime was followed, although the product was too soluble to be isolated as suggested.

The oxime (1.5 g.) was heated with 12 ml. of 85% sulfuric acid for 2 min. The clear colorless solution was poured into water, cooled, and made alkaline with potassium hydroxide. The precipitate of potassium sulfate was filtered off and the filtrate was extracted three times with chloroform. No residue remained after the evaporation of the chloroform. Evaporation of the water solution yielded a solid which was extracted with methyl alcohol in a Soxhlet extractor for 20 hr. Evaporation of the extract yielded 1.76 g. of white crystalline solid. This material chars but does not melt. It gives a negative sulfate ion test with barium chloride and shows a strong potassium flame when it is burned. Although this material was not further characterized, it is probably potassium 2-(2′-aminoethylsulfonyl)propionate.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

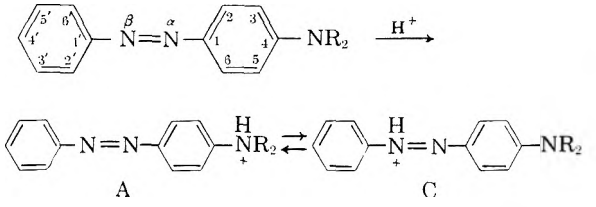
Physical Properties of Aminoazobenzene Dyes. V. The C_ϵ/A_ϵ Ratio[1]

EUGENE SAWICKI[2]

Received November 20, 1956

The tautomerism of 73 azobenzene derivatives in 50% ethanolic acid solution has been investigated. The reproducible, simply-obtained $C\epsilon/A\epsilon$ ratio gives a crude idea of the ratio of C (proton goes to β-nitrogen) to A (proton goes to amino nitrogen) tautomers present in acid solution. This $C\epsilon/A\epsilon$ ratio should prove to be very useful in the determination of structures of unknown azo dyes. The $C\epsilon/A\epsilon$ ratio has been correlated with basicity, resonance, inductive, steric and intra- and intermolecular hydrogen bonding effects. Approximately 100 spectra (310–600 mμ) in 50% alcoholic acid solution have been reported.

It has been shown that the 4-aminoazobenzene dyes exist in acid solution as a *p*H-dependent equilibrium mixture of tautomeric forms in which the ammonium, A, form of the salt is associated with a band near 320 mμ and the cationic resonating form, C, is associated with the long wave length band.[3]



The C_ϵ/A_ϵ ratio gives a crude idea of the tautomeric equilibrium. C_ϵ is the molar extinction coefficient at the wave length maximum of the C band; A_ϵ is the molar extinction coefficient at the wave length maximum of the A band.

In the 4-aminoazobenzene dyes there are two main basic centers—at the β-nitrogen and at the amino nitrogen. The diverse effects on, and the interplay between, these two resonance terminals determines the basicity of the molecule. Other things being equal, increasing the basicity of the β-nitrogen or decreasing the basicity of the amino nitrogen increases the value of the C_ϵ/A_ϵ ratio. For example, in the 4-*N*,*N*-dialkylaminoazobenzenes, the dimethyl compound, DAB, pK_a 2.28, has a C_ϵ/A_ϵ ratio of 3.62 while the *N*-methyl-*N*-benzyl compound, pK_a 1.6, has an increased C_ϵ/A_ϵ ratio of 4.5. The benzyl group has decreased the basicity of the amino nitrogen, thus causing an over-all decrease in the first pK_a. But this has caused the β-nitrogen to be proportionally stronger in basicity and thus a greater percentage of C tautomer is formed. In this manner the basicity of the amino nitrogen could be gradually decreased; this would cause a gradual increase in the C_ϵ/A_ϵ ratio until eventually only the C tautomer would be present in solution. On the other hand in 4-methylethylaminoazobenzene, pK_a 2.58, the C_ϵ/A_ϵ ratio drops to 1.4 because of the increase in the basicity of the amino nitrogen in relation to the β-nitrogen. In 4-diethylaminoazobenzene, pK_a 3.08, the further increase in the basicity of the amino nitrogen causes a further decrease in the C_ϵ/A_ϵ ratio to 0.5. In 3-methyl DAB, pK_a 3.48, the steric effect of the 3-methyl group causes a further increase in the basicity of the amino group and a decrease in the C_ϵ/A_ϵ ratio to 0.025. This same regular effect is seen in many of the derivatives of the 4-dialkylaminoazobenzenes (compare 2′-nitro DAB, 2′-nitro MEAB and 2′-nitro DEAB or the 3′-nitro, 4′-nitro, 4′-acetyl or 3′-methyldialkylaminoazobenzenes), Table I.

It has been shown that the 2-methyl group in 2-methyl DAB increases the electron density of the β-nitrogen,[4] thus causing an increase in the pK_a to 3.08 and an increase in the C_ϵ/A_ϵ ratio to 10.0. This same effect can be seen for eleven other 2-methyl DAB derivatives, Table I.

A 2′-methyl group decreases the basicity of the β-nitrogen; the over-all effect is a decrease in the pK_a and the C_ϵ/A_ϵ ratio of the 4-dialkylaminoazobenzene. In 2′-ethyl DAB the increased steric effect causes a further drop in the basicity and C_ϵ/A_ϵ ratio. There is a drop in basicity for 2′-chloro DAB and 2′-chloro MEAB as compared to the analogous 2′-methyl derivatives. This is not unexpected for the 2′-chloro group is more base-weakening than the 2′-methyl group.[5] In spite of this the C_ϵ/A_ϵ ratios of the 2′-chloro dyes are slightly higher than the ratios of the analogous methyl derivatives. One of the factors that probably contributes to this fairly high C_ϵ/A_ϵ ratio is the presence of weak intramolecular hydrogen bonding between the 2′-chloro and the hydrogen on the β-nitrogen of the C tautomer (*i.e.* the azonium hydrogen).

In 2′-methoxy DAB steric hindrance and the resonance interaction of the methoxy group with

(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Present address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(3) E. Sawicki, *J. Org. Chem.*, **21**, 605 (1956).

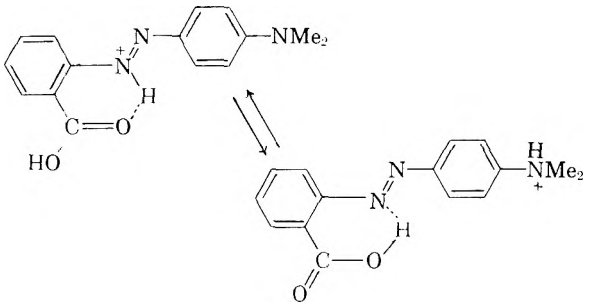
(4) E. Sawicki and F. Ray, *J. Org. Chem.*, 19, 1686 (1954); E. Sawicki and Gerber, *J. Org. Chem.*, 21, 410 (1956).

(5) J. Vandenbelt, C. Henrich, and S. Berg, *Anal. Chem.*, 26, 726 (1954).

the α-nitrogen would have a base-weakening effect on the β-nitrogen. Among other effects the intramolecular hydrogen bonding involving the methoxy oxygen and the azonium hydrogen of the C tautomer would increase the proportion of that tautomer present in acid solution. Consequently it is not surprising to find a C_ϵ/A_ϵ ratio of 2.36 for this compound.

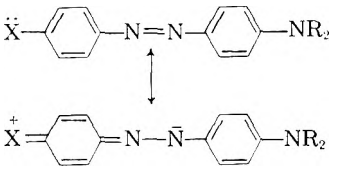
In 2′-nitroDAB the pK_a is 1.49. The powerful base-weakening inductive effect of the nitro group on the β-nitrogen and the base-weakening resonance effect on the amino nitrogen are two of the factors causing the decreased basicity. The first factor would strongly decrease the C_ϵ/A_ϵ ratio; the second factor would increase the ratio. The effect of the second factor and the formation of an intramolecular hydrogen bond between the nitro group and the azonium hydrogen would help to explain the fairly high C_ϵ/A_ϵ ratio of 1.6 for this compound.

2′-CarboxyDAB in acid solution shows a large increase in the C_ϵ/A_ϵ ratio. This can only mean that in this salt the intramolecular hydrogen bond between a carboxyl oxygen and the azonium hydrogen is strong enough to force the equilibrium C $\rightleftarrows$ A far to the left.

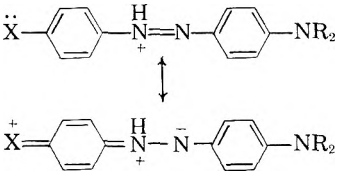


An electron-donor group in the 3′-position of a 4-dialkylaminoazobenzene increases the C_ϵ/A_ϵ ratio by an amount which appears to depend upon the substituent's electron-donor strength. For example, while DAB has a C_ϵ/A_ϵ ratio of 3.62, 3′-methylDAB has a ratio of 4.1, and 3′-ethoxyDAB has a ratio of 4.5. The inductive effect has apparently increased the electron density of the β-nitrogen. This point needs a more thorough investigation. An electron attracting group in the 3′-position has little, if any, effect on the ratio.

As the electron-donor strength of a group in the 4′-position of a 4-dialkylaminoazobenzene increases from hydrogen to methoxy, the C_ϵ/A_ϵ ratio decreases and the C band shifts toward the visible. For example, DAB has λ_{max} 516 mμ and a C_ϵ/A_ϵ ratio of 3.62; 4′-methylDAB has λ_{max} 531 mμ and a C_ϵ/A_ϵ ratio of 2.57; 4′-acetylaminoDAB has λ_{max} 545 mμ and a C_ϵ/A_ϵ ratio of 1.86; 4′-methoxyDAB has λ_{max} 548 and a C_ϵ/A_ϵ ratio of 1.00. This same order is seen in 2-methylDAB, 2,4′-dimethylDAB and 2-methyl-4′-acetylaminoDAB. The decrease in the C_ϵ/A_ϵ ratio is apparently due to the following resonance effect which would cause a slight increase in the electron density at the α-nitrogen[6] and a consequent decrease in the electron density at the β-nitrogen thus:



The shift of the C band towards the visible in these 4′-substituted derivatives is probably due to the following type of extra-conjugative resonance in the C tautomer.



The direct relation between these two resonance effects is obvious. The drop in the C_ϵ/A_ϵ ratio and the shift towards the visible on substitution of an electron-donor group in the 4′- or 2′-position[7] must be due to a resonance phenomenon for a similar substitution in the 3′-position of a 4-dialkylaminoazobenzene causes neither a strong red shift nor a decrease in the C_ϵ/A_ϵ ratio, Table I. For example, 2′-methoxyDAB, λ_{max} 540, 4′-ethoxyDAB, λ_{max} 552, and 4′-acetylaminoDAB, λ_{max} 545, show a definite red shift in dilute acid solution as compared to 3′-ethoxyDAB, λ_{max} 521, DAB, λ_{max} 516, and 3′-acetylaminoDAB, λ_{max} 518.

A 4′-halogen apparently increases the electron density of the α-nitrogen through a resonance effect. Consequently substitution of a halogen in the 4′-position of a 4-dialkylaminoazobenzene causes decreases in the C_ϵ/A_ϵ ratio and the basicity of the molecule.

As the electron-attractor strength of a group in the 4′-position of a 4-dialkylaminoazobenzene increases from hydrogen to nitro, the C_ϵ/A_ϵ ratio decreases and the long wave length zwitterionic resonance, or Z, band of the compound in alcoholic solution shifts toward the visible. For example, DAB has λ_{max} 408 mμ and a C_ϵ/A_ϵ ratio of 2.57; 4′-thiocyanoDAB[8] has λ_{max} 433 mμ and a C_ϵ/A_ϵ ratio of 4.54; 4′-acetylDAB has λ_{max} 447 mμ and a

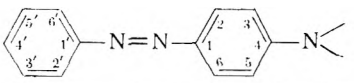
(6) For more powerful electron-donors, such as the alkylthio or amino groups the electron density at the α-nitrogen would be expected to be large enough for this nitrogen to seriously compete with the β- and amino nitrogens for the proton.

(7) However in the 2′-position steric, inductive and intramolecular hydrogen bonding effects could also be of some importance.

(8) The thiocyano group has been shown to be electron-attracting through basicity [M. Rogers, T. Campbell, and R. Maatman, *J. Am. Chem. Soc.*, **73**, 5122 (1951)] and electric moment data [T. Campbell and M. Rogers, *J. Am. Chem. Soc.*, **70**, 1029 (1948)].

TABLE I

C_e/A_e RATIOS OF 4-AMINOAZOBENZENE DYES



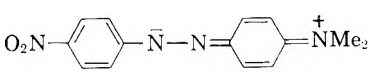
Compound	pK_a[a]	λ_{max}[b], mμ(ε × 10^{-3}) C Band	A Band	HCl, Normality	$\frac{C_e}{A_e}$
2-AB[c]	1.8	....	328[d](20.3)	1.0	0.00
4',5-diMe-2-AB	2.5	....	350[e](23.6)	1.0	0.00
3-AB	3.0	....	320[f](18.0)	1.2	0.00
4-AB	2.28	500(12.2)	318–320(16.8)	1.0	0.73
		500(16.5)	318–320(15.8)	2.0	1.0
		500–504(36.7)	318–320(9.16)	6.0	4.0
2,3'-diMe-4-AB	2.92	500(31.0)	330(10.0)	1.0	3.1
2,4'-diMe-4-AB	2.92	510(26.0)	332(12.2)	1.0	2.1
3,4'-diMe-4-AB	2.39	510(17.5)	330–332(16.9)	1.0	1.0
2',3-diMe-4-AB	2.29	488–490(2.40)	326(19.1)	1.0	0.13
MAB[g]	2.37	505(40.9)	320(7.64)	1.2	5.4
3'-MeMAB	2.43	510–512(42.6)	320–322(7.40)	1.2	5.8
EAB[h]	2.58	512–516(36.3)	318–320(9.96)	1.2	3.6
DAB[i]	2.28	514–520(34.0)	320(10.14)	0.6	3.4
		512–520(35.5)	320(9.8)	1.2	3.6
		514–518(40.3)	320(8.10)	3.0	5.0
		516–520(47.3)	322–324(5.26)	6.0	9.0
MEAB[j]	2.58	516(21.5)	318(15.2)	1.0	1.4
		516(23.6)	318(14.4)	2.0	1.6
DEAB[k]	3.08	518(9.50)	318(19.5)	1.0	0.49
		517(10.8)	318(19.2)	2.0	0.56
MBAB[l]	1.6	526(41.2)	318–324(9.20)	1.2	4.5
3-MeDAB	3.48	500[m](0.50)	319(19.8)	1.0	0.025
4'NO_2-3-MeDAB		490–494(1.02)	328(25.5)	3.0	0.040
		506–510(1.26)	328(25.2)	6.0	0.050
4'-Ac-3-MeDAB	3.27	484–486(0.984)	325(28.3)	0.6	0.035
		494–496(1.07)	325–327(27.9)	3.0	0.038
		510–512(1.29)	325(27.7)	6.0	0.047
3'-NO_2-3-MeDAB	3.18	~500[n](0.34)	310(22.4)	1.2	0.015
2-MeDAB	3.08	514(48.2)	326–328(4.82)	1.2	10.0
		514–516(49.9)	328(4.20)	3.0	11.9
		514–515(53.0)	330–334(3.14)	6.0	16.9
2,2'-DiMeDAB	2.64	510(15.3)	332(13.8)	1.0	1.1
2'-Me-2'-COOHDAB		516(52.5)	336(4.20)	3.0	12.5
2-Me-2'$COOCH_3$DAB		510–514(51.5)	336–338(4.16)	0.6	12.4
		512–514(51.8)	332–336(4.10)	1.2	12.6
		516(51.0)	336(4.00)	3.0	12.8
		514–520(53.1)	336–338(3.58)	6.0	14.8
2-Me-2'-NO_2DAB	2.12	502–510(40.0)	318–320(8.6)	1.2	4.7
2-Me-3'-Cl-DAB	2.67	506–508(48.1)	328–330(5.04)	1.2	9.5
2-Me-3'-AcDAB	2.73	504–508(49.4)	324(5.56)	1.2	8.9
2,4'-DiMeDAB		530(45.2)	334–336(6.60)	1.2	6.9
		530(48.0)	336–338(5.44)	3.0	8.8
2-Me-4' AcDAB	2.88	510(62.1)	320(5.68)	1.2	10.9
		514–516(63.4)	320(5.64)	3.0	11.2
2-Me-4'-NO_2DAB		510(56.3)	340(5.72)	1.2	9.8
		510(66.0)	340–342(5.40)	3.0	12.2
2-Me-4'-NHAcDAB		545(44.5)	352–357(8.60)	1.2	5.2
2'-MeDAB	2.04	515(5.10)	325(17.6)	1.2	0.29
2'-EtDAB	1.85	510(2.60)	332(18.1)	1.0	0.14
2'-OMeDAB	2.20	540(21.0)	320[o](8.90)	1.0	2.4
		540(25.5)	318[o](8.16)	3.0	3.1
2'-ClDAB	1.74	500(5.40)	320(17.0)	1.0	0.32
2'-NO_2DAB	1.5	509(19.8)	315(12.4)	1.0	1.6
2'-COOHDAB		518(43.4)	325–330(3.32)	1.2	13.1
2'-MeMEAB		505–510(2.24)	328(19.2)	1.2	0.12
2'-Cl-MEAB	2.14	500(2.50)	320–324(17.8)	1.2	0.14
2'-NO_2-MEAB	1.75	508(10.7)	320(15.0)	1.0	0.7
2',5'-DiMeDAB	2.0	520(5.70)	327(16.7)	1.0	0.34
2',4',6'-TriBrDAB	1.0	450(4.20)	315(10.0)	1.0	0.42
		460–465(8.10)	315(9.80)	6.0	0.83
3'-MeDAB	2.33	522–526(37.6)	320–326(9.2)	1.2	4.1
3'-EtODAB		520–522(36.6)	318(8.16)	1.2	4.5

TABLE I (*Continued*)

3′-NHAcDAB	2.27	518(36.2)	318(9.16)	1.2	4.0
3′-ClDAB	2.01	510–514(35.3)	316–318(9.96)	1.2	3.6
3′-AcDAB	2.03	509(37.3)	312–318(10.3)	1.2	3.6
3′-NO_2DAB	1.67	500(37.8)	310–312(10.52)	1.2	3.6
3′-CF_3DAB	1.84	500(34.4)	312–314(10.76)	1.2	3.2
3′-MeMEAB		518–524(23.7)	322–326(13.84)	1.2	1.7
3′-NHAcMEAB	2.47	520(22.2)	315(13.6)	1.2	1.6
3′-ClMEAB		510–512(22.2)	318(15.0)	1.0	1.5
3′-AcMEAB	2.28	510(21.2)	316(14.4)	1.0	1.5
3′-NO_2MEAB	2.0	500(23.6)	312–314(15.2)	1.2	1.6
3′-CF_3MEAB	2.15	504–506(20.5)	314(15.4)	1.2	1.3
3′-MeDEAB		520(11.16)	322–324(18.8)	1.2	0.59
3′-NO_2DEAB	2.39	502–504(10.8)	310–314(19.36)	1.2	0.56
4′-MeDAB	2.36	530–532(31.7)	330–334(12.32)	1.2	2.6
		532(45.3)	332–334(6.60)	6.1	6.9
4′-EtDAB	2.30	530–534(31.7)	332–334(12.4)	1.2	2.6
		532–534(45.7)	334(6.60)	6.1	6.9
4′-*i*-PrDAB	2.31	532–534(32.3)	330–336(12.52)	1.2	2.6
		532–534(46.0)	334–338(6.8)	6.1	6.8
4′-MeODAB	2.40	548(18.5)	352(18.2)	1.2	1.0
		550(20.0)	352(17.1)	2.0	1.2
4′-EtODAB		550–554(18.8)	354(18.8)	1.2	1.0
4′-NHAcDAB	2.25	545(28.3)	352(15.2)	1.2	1.9
4′-FDAB	2.00	517(21.4)	320(14.4)	1.(	1.5
4′-SCNDAB		516(44.3)	330(9.76)	1.2	4.5
4′-AcDAB	2.16	516–524(58.4)	320(7.76)	1.2	7.5
		512–518(59.4)	320(7.12)	3.0	8.3
4′-NO_2DAB	1.81	512(61.6)	332(7.10)	1.0	8.7
4′-EtMEAB	2.72	532(13.7)	333(14.4)	1.0	0.95
4′-FMEAB	2.40	519(10.8)	320(17.8)	1.0	0.61
4′-AcMEAB	2.35	515(46.3)	322(11.44)	1.2	4.0
		515–517(50.8)	320(10.4)	3.0	4.4
4′-NO_2MEAB		506(67.8)	328(10.04)	1.2	6.8
4′-AcDEAB		515(29.3)	322–325(17.72)	1.2	1.7
4′-NO_2DEAB		510(40.0)	325–327(15.8)	1.2	2.5

[a] Reference 3. [b] Determined from 300 to 600 mμ in 50% alcoholic hydrochloric acid. [c] AB is aminoazobenzene. [d] Two shoulders are found at 410 and 570 mμ. In 50% alcoholic 6*N* hydrochloric acid these shoulders are intensified into bands—one at 420 mμ, ε 900, due to the R band analogous to the R band of azobenzene, the other at 570 mμ, ε 738 either due to an impurity or a slight amount of C tautomer. [e] As in 2-AB two weak bands are found at 430 and 600 mμ. [f] Band is also found at 430 mμ, ε 810 which is an R band. [g] MAB is 4-methylaminoazobenzene. [h] EAB is 4-ethylaminoazobenzene. [i] DAB is 4-dimethylaminoazobenzene. [j] MEAB is 4-methylethylaminoazobenzene. [k] DEAB is 4-diethylaminoazobenzene. [l] MBAB is 4-methylbenzylaminoazobenzene. [m] Band at 444 mμ, ε 630 is an R band. All underlined values are shoulders. [n] Determined for comparison. Band at 452 mμ, ε 550 is an R band. [o] Another A band is found at 360 mμ, ε 7200.

C_ϵ/A_ϵ ratio of 7.52; 4′-nitroDAB has λ_{max} 477 and a C_ϵ/A_ϵ ratio of 8.7. This same relation is seen for the 4′-acetyl and 4′-nitro derivatives of MEAB and DEAB. The increase in the C_ϵ/A_ϵ ratio is probably caused by an increase in the electron density of the β-nitrogen and a decrease in the basicity of the amino nitrogen. This decrease in basicity and the shift of the Z band toward the visible most likely stems from the greater contribution in the ground state (as compared to DAB) of the zwitterionic resonance structure



Comparison of the C_ϵ/A_ϵ ratios of 4-amino-, 4-alkylamino- and 4-dialkylamino-azobenzenes discloses that the C_ϵ/A_ϵ ratios decrease in the order $-NHR > NR_2 > NH_2$. Apparently at least two opposing factors are at work. The alkyl groups would tend to increase the electron density of the amino nitrogen through an inductive effect and would tend to decrease the electron density of the amino nitrogen because of the decrease in solvation energy stabilization since the alkyl groups do not form hydrogen bonds with the solvent molecules.[9]

Isomeric alkyl derivatives are usually difficult to differentiate, but by use of the C_ϵ/A_ϵ ratio the five monomethyl-DAB isomers can be readily distinguished, Table I.

EXPERIMENTAL

Preparations. All the dyes were available from other investigations in this laboratory and had been purified by numerous crystallizations from two to five different solvents.[4] Chromatography was used where necessary.

Absorption spectral data. The spectra of all compounds were measured with a Beckman Model DU Spectrophotometer from 300 to 600 mμ in 50% alcoholic 1.2*N* hydrochloric acid solution, unless otherwise stated. This solution consisted of 50 ml. of 2.4*N* aqueous hydrochloric acid (200 ml. of concentrated hydrochloric acid diluted to 1000 ml. with distilled water) and the necessary volume of a 95% alcoholic solution of the azo dye, diluted to 100 ml. with commercial 95% ethanol.

Most of the C_ϵ/A_ϵ ratio values have been obtained at a

(9) A. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949).

hydrochloric acid normality of 1.0 or 1.2. At this normality the vast majority of the 4-aminoazobenzene dyes show slight changes in the C_ϵ/A_ϵ ratio with a change in normality. For more basic compounds (such as 4'-amino DAB) this ideal plateau would be found at a lower normality. The ideal situation would be to obtain C_ϵ/A_ϵ values at the lowest normality at which a 100% of the monocationic salt was present. It is felt that the determination of the C_ϵ/A_ϵ ratio at a normality of 1.0 to 1.2 in most cases is close to the ideal situation and, although less accurate, is a much simpler procedure. Consequently it would be of greater value for the determination of the structure of an unknown azo dye.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

Ultraviolet-Visible Absorption Spectra of Quinoxaline Derivatives[1]

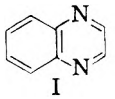
EUGENE SAWICKI,[2] BARBARA CHASTAIN, HAZEL BRYANT, AND ALBERT CARR

Received December 6, 1956

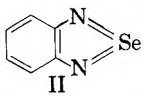
Over forty ultraviolet-visible absorption spectra of fifteen quinoxaline derivatives have been determined in alcoholic and acidic solutions. The spectra and the structure of the cations are discussed. Several new quinoxaline derivatives have been prepared.

In a previous paper[3] a number of 2,1,3-benzoselenadiazoles or piaselenoles, were prepared as possible purine antagonists. The spectra of the piaselenole derivatives were also investigated in the hope of shedding more light on the spectral properties of biologically important heterocyclic ring systems. For this reason it was decided to investigate the spectral properties of the quinoxalines, which are potential folic acid antagonists.

If one considers the tetravalent organoselenium atom, =Se=, as being somewhat similar to the =CH—CH= group, then a striking resemblance is evident between quinoxaline, I, and the tetravalent selenium structure of piaselenole, II. Like the



I



II

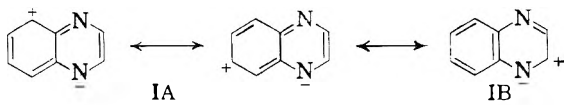
piaselenoles, quinoxaline derivatives form monocationic and dicationic salts. The dicationic salts usually absorb at the longest wave length and the bases at the shortest wave length.

In 2,3-dimethyl- or 2,3-diphenyl-quinoxaline substitution of an electron-donor group in the 6-position causes an increasing bathochromic shift in the order H < OCH_3 < C_6H_5 < SCH_3 < NH_2 for the base and monocationic forms and, except for the more strongly basic amino compound, for the dicationic compounds, Table I. The same order has been found for the analogously substituted 2,1,3-benzoselenadiazole derivatives[3] and in *para* substituted triphenylmethane dyes.[9] The fused benzene ring in 2,3-diphenyl-1,4-diazaanthracene is approximately equivalent in electron-donor properties to the 6-methoxy group as shown by the spectral data, Table I.

The sequence of proton addition in the 6-substituted quinoxalines (in the absence of an amino group) is shown in the spectra of 6-methylthio-2,3-diphenylquinoxaline, Fig. 1. In the important zwitterionic resonance structures of this compound, the 4-nitrogen is the electron-attracting resonance terminal and consequently has the greatest electron density and thus attracts the first proton.

In 2,3-symmetrically disubstituted quinoxalines the bathochromic shift increases in the series H < CH_3 < C_6H_5 < $C_6H_4OCH_3$ < $C_6H_3O_2CH_2$ < CH = CH — C_6H_5 < $(CH = CH)_2C_6H_5$[10] < $(CH = CH)_3C_6H_5$.[10]

Some of the zwitterionic resonance forms which are strong contributors to the excited state are



IA IB

Thus substitution of an electron-donor group in the 2,3,5,6,7 or 8 positions should cause the excited state structure to be of lower energy than IA or IB because the substituent(s) would accept the positive charge much more readily than would the unsubstituted position and consequently the compound(s) would absorb at longer wavelength.

The quinoxaline derivatives formed monocationic salts in 50% alcoholic 6*N* hydrochloric acid with the exception of the amino derivatives which

(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Present address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(3) E. Sawicki and A. Carr, *J. Org. Chem.*, **22**, 503 (1957).

(4) R. Bost and E. Towell, *J. Am. Chem. Soc.*, **70**, 903 (1948).

(5) H. Goldstein and M. Streuli, *Helv. Chim. Acta*, **20**, 650 (1937).

(6) F. Bell and J. Kenyon, *J. Chem. Soc.*, 2708 (1926).

(7) H. Gilman and H. Broadbent, *J. Am. Chem. Soc.*, **70**, 2619 (1948).

(8) G. Bennett and G. Willis, *J. Chem. Soc.*, 1960 (1928).

(9) N. Deno, J. Jaruzelski, and A. Schriesheim, *J. Org. Chem.*, **19**, 155 (1954).

(10) F. Bohlmann, *Chem. Ber.*, **84**, 860 (1951).

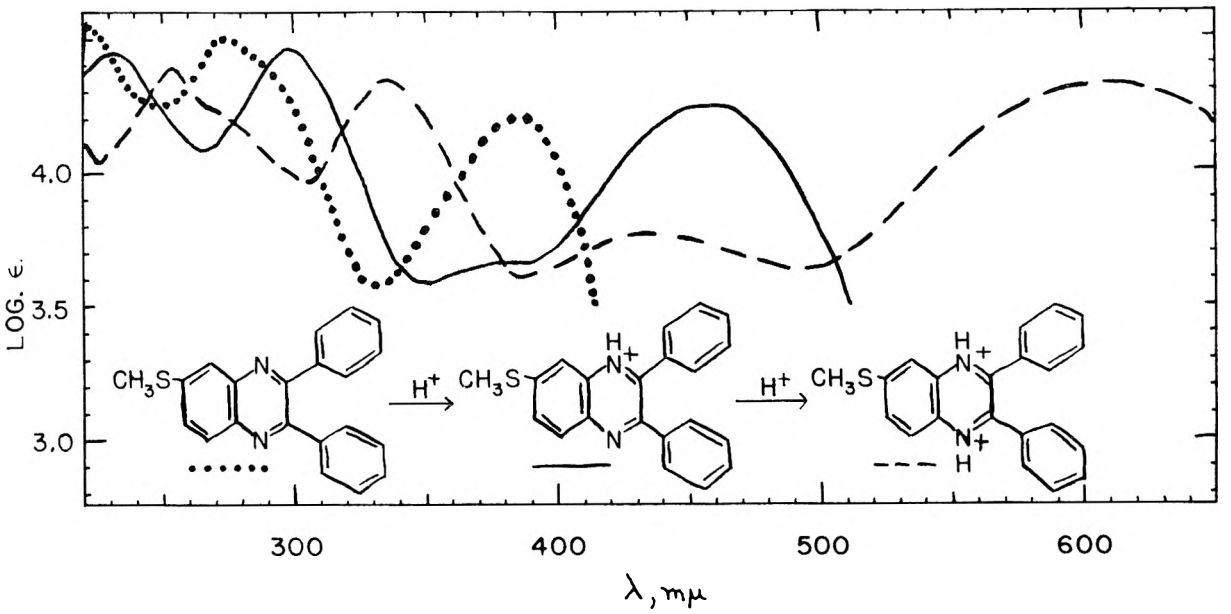
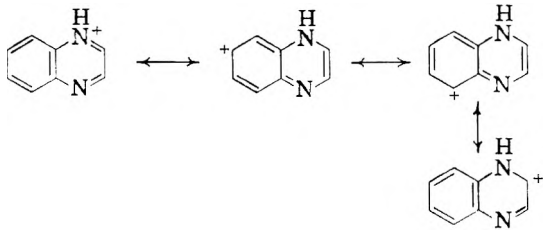


Fig. 1. Ultraviolet-visible Absorption Spectra of 2,3-Diphenyl-6-methylmercaptoquinoxaline in 95% Ethanol (.....); 50% Alcoholic 6*N* Hydrochloric Acid (—·——·) and 95% Sulfuric Acid (– – – –).

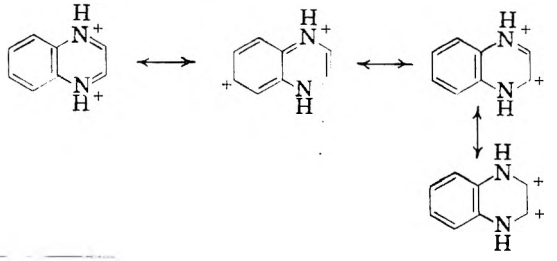
will be subsequently discussed. In the monocationic compounds the cationic resonating structures contributing to the overall structure are



Because of a lack of separation of charge, there is a bathochromic shift as compared to the analogous base.

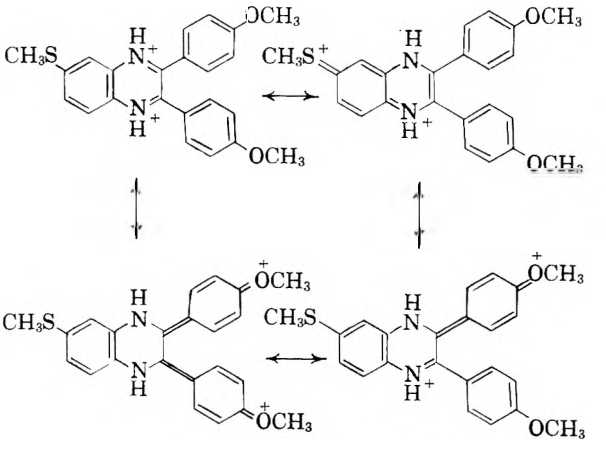
The quinoxaline derivatives formed dicationic salts in 95% sulfuric acid except for the amino compounds which formed tricationic salts. Bennett and Willis[11] have reported the color in sulfuric acid of some 28 2-styryl- and 2,3-distyryl quinoxaline derivatives substituted in the styryl benzene ring. The effect of increasing the length of conjugation by a CH=CH group in the dicationic symmetric salts is to push the long wave length band approximately 60–100 mμ into the visible.

In the dicationic compounds some of the dicationic resonating structures contributing to the overall structure are



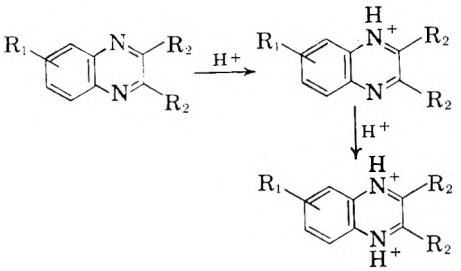
(11) G. Bennett and G. Willis, *J. Chem. Soc.*, 256 (1929).

The bathochromic shift in these salts is apparently due to the greater amount of resonance in the excited state compared to the analogous monocationic salts. Substitution of electron-donor groups in both the aromatic and heterocyclic rings causes a much greater bathochromic shift than the presence of similar electron-donor groups in only the aromatic or heterocyclic rings, Table I. In this respect 2,3-bis-4′-methoxyphenyl-6-methylthioquinoxaline absorbs at the longest wave length in strong acid solution, Table I. Some of the dicationic resonating structures which account for the long wave length absorption of this compound in 95% sulfuric acid are shown below.



The spectra of the aminoquinoxalines in strong acid solution are exceptional because of the greater basicity of the amino group as compared to the phenyl, methoxy, or methylthio groups. The spectrum of 6-amino-2,3-diphenylquinoxaline, III, in alcohol contains a long wavelength band at 407 mμ which shifts to 492 mμ in 50% alcoholic 1.2*N* hydrochloric acid, Fig. 2 and Table I. In the same

TABLE I



R_1	R_2	M.P., °C.	λ_{max} (log ϵ) 95% EtOH	50% EtOH 6*N* HCl	95% H_2SO_4
H	CH_3	105–106[a]	237 (4.39)[b]	247 (4.42)	220 (3.96)
			315 (3.84)	340 (4.03)	255 (4.42)
					362 (4.17)
6-CH_3O	CH_3	99–100[a]	248 (4.28)	260 (4.27)	268 (4.29)
			340 (3.91)	340[c] 3.66)	370 (3.85)
				377 (3.91)	448 (3.90)
6-CH_3S	CH_3	76–78	262 (4.39)	225 (4.32)	237 (4.30)
			360 (3.86)	280 (4.30)	306 (4.31)
				340 (3.38)	380 (3.43)
				419 (3.87)	560 (3.95)
H	C_6H_5	124–125[a]	244 (4.53)[b]	255 (4.53)	225 (4.19)
			265 (4.36)	280 (4.08)	270 (4.50)
			345 (4.07)	390 (4.13)	*380* (3.72)
					470–475 (4.16)
H	C_6H_5, 4′-$C_6H_4NMe_2$	121–122[a]	235 (4.54)	245 (4.62)[d]	220 (4.18)
			310 (4.26)	265 (4.35)	270 (4.46)
			406–409 (4.06)	345 (4.07)	375 (3.73)
				410 (2.54)	460 (4.11)
				530–535 (2.21)	
6.7-$(CH)_4$	C_6H_5	187–189[e]	232 (4.59)	240 (4.58)	252 (4.44)
			275 (4.72)	295 (4.60)	325 (4.46)
			305 (4.52)	422 (4.28)	510 (4.36)
			388 (4.10)		
6-CH_3O	C_6H_5	155–156[a]	228 (4.43)	~224 (4.35)	254 (4.33)
			255 (4.52)	270 (4.43)	284 (4.32)
			275 (4.30)	420 (4.21)	300 (4.21)
			366 (4.15)		400 (3.69)
					516–520 (4.29)
6-C_6H_5	C_6H_5	148[f]	268 (4.62)	233 (4.33)	255 (4.26)
			365 (4.02)	288 (4.51)	287 (4.30)
				418 (4.24)	324 (4.28)
					546–554 (4.26)
6-CH_3S	C_6H_5	144–145	272 (4.50)	232 (4.45)	253 (4.39)
			385 (4.20)	297 (4.46)	270 (4.22)
				378 (3.65)	335 (4.35)
				458 (4.23)	435 (3.76)
					610 (4.31)
6-NH_2	C_6H_5	176–178[g]	245 (4.37)	242 (4.41)[h]	225 (4.29)
			265 (4.35)	294 (4.30)	270 (4.50)
			292 (4.41)	355 (3.84)	380 (3.75)
			407 (4.00)	492 (4.00)	480 (4.15)
5-NH_2-7-Cl[d]	C_6H_5	214–215	230 (4.37)	247 (4.47)[i]	230 (4.22)
			267 (4.27)	270 (4.25)	262 (4.31)
			305 (4.55)	290 (4.17)	282 (4.15)
			355 (3.64)	355 (4.03)	435–440 (4.07)
			402 (3.40)	520 (2.64)	520 (3.45)
H	4-CH_3O-C_6H_4	148–149[a]	250 (4.63)	222 (4.51)	545 (4.21)[j]
			282 (4.29)	265 (4.51)	
			370 (4.15)	300 (4.15)	
				435 (4.15)	

TABLE I (*Continued*)

H	3,4-CH_2O_2-C_6H_3	199–200[k]	224 (4.63) 247 (4.44) 265 (4.34) 295 (4.12) 375 (4.09)	230 (4.51) 255 (4.34) 290 (4.26) 447 (4.02)	555–570 (4.09)[j]
H	C_6H_5CH=CH	193–194[l]	304 (4.64)[b] 345 (4.38) 395 (4.26)	230 (4.29) 310 (4.48) 448 (4.29)	240 (4.17) 342 (4.30) 370 (4.20) 546–554 (4.33)
6-CH_3S	4-CH_3O-C_6H_4	144–145	220 (4.58) 225 (4.59) 240 (4.39) 275 (4.53) 285 (4.49) 396 (4.30)	226 (4.39) 265 (4.20) 296 (4.38) 396 (3.55) 480 (4.29)	245 (4.20) 290 (4.26) 320 (4.26) 348 (4.30) 480–490 (3.82) 650 (4.43)

[a] Reference 4. [b] In methanol—F. Bohlmann, *Chem. Ber.*, **84**, 860 (1951). [c] All underlined values are shoulders. [d] In 50% alcoholic 0.1*N* hydrochloric acid. In 50% alcoholic 1.2*N* hydrochloric acid λ_{max} (log ϵ) values are 255 (4.54); 280 (4.15); 384 (4.16). [e] Reference 5. [f] Reference 6. [g] Reference 7. [h] In 50% alcoholic 1.2*N* hydrochloric acid. In 50% sulfuric acid λ_{max} (log ϵ) values are 254 (4.44); 290 (3.99); 405 (4.03). [i] In 50% alcoholic 1.2*N* hydrochloric acid. In 50% sulfuric acid λ_{max} (log ϵ) values are 228 (4.35); 260 (4.46); 280 (4.20); 417 (4.17). [j] Unstable solution. Spectrum below 360 mμ not determined. [k] Reference 3. [l] Reference 8.

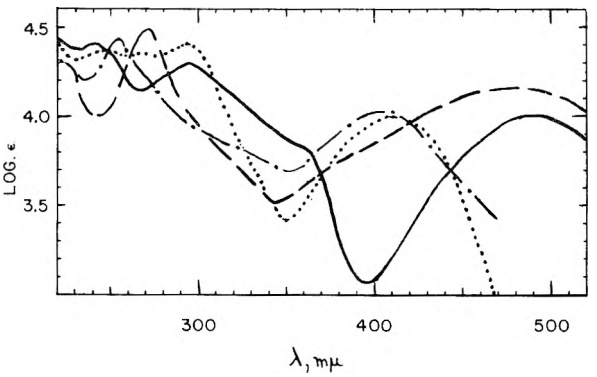
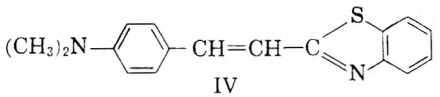
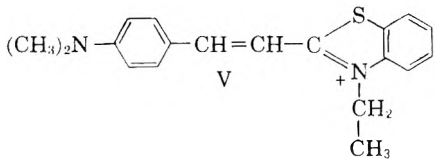


Fig. 2. Ultraviolet-visible Absorption Spectra of 2,3-Diphenyl-6-aminoquinoxaline in 95% ethanol (.....); 50% alcoholic 1.2*N* hydrochloric acid (——); 50% sulfuric acid (—·—·); and 95% sulfuric acid (----).

manner the base 2-*p*-dimethylaminostyrylbenzothiazole, IV, λ_{max} 400 mμ, absorbs at a much shorter wave length than its ethiodide, V, λ_{max} 524 mμ, when compared in methyl alcoholic solution.[12]

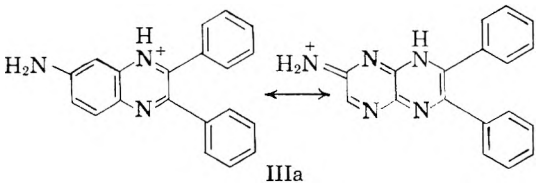


IV



V

Both the bases, III and IV, contain a zwitterionic resonance system (associated with the long wave length band at about 400 mμ) involving a chain of 9 atoms with the electron-donor amino nitrogen and the electron attractor heterocyclic nitrogen (*e.g.*, the 4-nitrogen of III) as the main resonance terminals. On the other hand V, the monocationic form of IV, involves a lower energy cationic resonating system with the amino and heterocyclic nitrogens as resonance terminals. Unlike the salts there is an expenditure of energy necessary for the separation of charge in the excited state of the bases. Thus, in the salt there is a "closing up" of energy levels as compared to the base. This explains the absorption at longer wave length of the salts as compared to the bases. In the same way III in 1.2*N* hydrochloric acid must contain the monocationic salt, IIIa, with a resonance system fairly similar to V, *e.g.*, IIIa.



IIIa

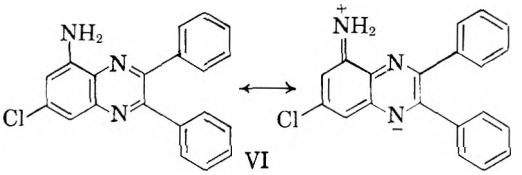
It is possible that in this same solution the tautomer involving proton addition to the amino nitrogen might be present to a smaller extent. This is implied by the presence of the strong shoulder at 355 mμ. The iso-*pi*-electronic 2,3-diphenylquinoxaline has its long wave length band at 345 mμ.

The spectrum of III in 50% sulfuric acid is closely similar to the spectrum of the monocationic salt of 2,3-diphenylquinoxaline in 50% alcoholic 6*N* hydrochloric acid, Table I. Consequently the second proton must add to the amino nitrogen of III. The spectrum of III in 95% sulfuric acid is closely similar to the spectrum of the dicationic salt of 2,3-diphenylquinoxaline in the same solvent. This means that in this strong acid solution a third proton must add to the remaining basic nitrogen of III.

In 2,3-diphenyl-5-amino-7-chloroquinoxaline, VI,

(12) L. Brooker and R. Sprague, *J. Am. Chem. Soc.*, **63**, 3203 (1941).

the zwitterionic resonance system associated with the long wavelength band contains an *o*-quinone ring system, *e.g.*



VI

The proton could be expected to add to the 1-nitrogen, but, just as in 2-aminoazobenzene as compared to 4-aminoazobenzene, and 4-aminopiaselenole as compared to 5-aminopiaselenole, the basicity of the electropositive amino nitrogen as compared to the electronegative nitrogen in the compounds containing an *o*-quinone zwitterionic resonance system is proportionally greater than the analogous basicities of the compounds containing the *p*-quinone zwitterionic resonance system. For example, the addition of the first proton to 4-aminopiaselenole goes to the amino nitrogen while in 5-aminopiaselenole it goes to the 3-nitrogen.[3] In 2-aminoazobenzene the first proton adds to the amino nitrogen while in 4-aminoazobenzene a mixture of monocationic tautomers is obtained consisting of two tautomers, one with the proton added to the amino nitrogen and the other with a proton attracted to the azo nitrogen furthest from the amino nitrogen.[13]

Fitting in with all these data the absorption spectrum of VI in 50% alcoholic 1.2*N* hydrochloric acid shows the presence of two tautomers, the minor one involving proton addition to the 1-nitrogen and containing bands at 520 and 300 mμ, and the other involving proton addition to the amino nitrogen with bands at 355 and 245 mμ and a shoulder at about 270 mμ. This latter tautomer would be expected to be closely similar spectrally to 2,3-diphenylquinoxaline which has bands at 345 and 244 mμ and a shoulder at 265 mμ (Table I). The spectrum of VI in 95% sulfuric acid has a strong band at 440 mμ which is due to the presence of a large amount of the dicationic salt and a weaker shoulder at about 520 mμ which is due to the tricationic salt. Except for the latter shoulder, the spectrum is closely similar to the spectra of the dicationic salt of VI and the monocationic salt of 2,3-diphenylquinoxaline. In the 4-amino compound the addition of the third proton is strongly repelled because of the resulting steric hindrance and neighboring positive charges.

2-4′-Dimethylaminophenyl-3-phenylquinoxaline in 50% alcoholic 0.1*N* hydrochloric acid has an ultraviolet spectrum closely similar to the spectrum of 2,3-diphenylquinoxaline in alcohol, Table I. This means that the first proton adds to the amino nitrogen. The two weak bands in the visible are due either to impurities or possibly to a very small amount of the tautomer involving proton addition to the 1-nitrogen. In 50% alcoholic 1.2*N* hydrochloric acid a second proton adds to give a dicationic salt (with a proton on the amino nitrogen and a proton possibly on the 4-nitrogen) closely similar spectrally to the monocationic salt of 2,3-diphenylquinoxaline. In 95% sulfuric acid a tricationic salt is formed iso-*pi*-electronic and spectrally similar to the dicationic salt of 2,3-diphenylquinoxaline, Table I.

(13) E. Sawicki, *J. Org. Chem.*, 21, 605 (1956).

EXPERIMENTAL[14]

2,3-Diphenyl-5-amino-7-chloroquinoxaline. A fine suspension of 18.8 g. of 1,2-diamino-3-nitro-5-chlorobenzene was added to a solution of 90 g. of stannous chloride dihydrate in 100 ml. of concentrated hydrochloric acid. The solution was evaporated to one-half volume, cooled, and filtered. The crystals were washed with concentrated hydrochloric acid, methanol, and then ether. Twenty-one grams of 1,2,3-triamino-5-chlorobenzene dihydrochloride was obtained.

Equivalent amounts of the dihydrochloride and benzil were allowed to react in aqueous methanol. Two crystallizations from ethanol gave a 75% yield of bright yellow crystals of the quinoxaline, m.p. 214–215°. The compound had a green fluorescence in acetone.

Anal. Calcd. for $C_{20}H_{14}ClN_3$: N, 12.7. Found: N, 12.5.

2,3-Dimethyl-6-methylthioquinoxaline. 1,2-Diamino-4-methylthiobenzene hydrochloride and 2,3-butanedione were reacted in aqueous methanol. Crystallization from hexane gave an 80–85% yield of yellow crystals, m.p. 76–78°.

Anal. Calcd. for $C_{11}H_{12}N_2S$: N, 13.7. Found: N, 13.8.

2,3-Diphenyl-6-methylthioquinoxaline. 1,2-Diamino-4-methylthiobenzene hydrochloride and benzil were allowed to react in aqueous methanol. Crystallization from heptane gave a 90% yield of bulky yellow crystals, m.p. 144–145°.

Anal. Calcd. for $C_{21}H_{16}N_2S$: C, 76.8; H, 4.88; N, 8.54. Found: C, 76.5; H, 4.81; N, 8.50.

2,3-Di-4′-methoxyphenyl-6-methylthioquinoxaline. Equivalent amounts of 1,2-diamino-4-methylthiobenzene hydrochloride and *p*-anisil were refluxed in acetic acid for 30 min. Addition of excess water and fractional crystallization of the precipitated solid from heptane gave 40–50% yield of yellow needles, m.p. 144–145°.

Anal. Calcd. for $C_{23}H_{20}N_2O_2S$: N, 7.22. Found: N, 7.15.

Absorption spectral data. The spectra of all compounds were measured with a Beckman Model DU spectrophotometer. The 50% alcoholic 6*N* hydrochloric acid solution consisted of 50 ml. of concentrated hydrochloric acid diluted to 100 ml. with 95% ethanol; 50% sulfuric acid consisted of 50 ml. of concentrated sulfuric acid diluted to 100 ml. with 95% ethanol; 95% sulfuric acid consisted of 5 ml. of 95% ethanol diluted to 100 ml. with concentrated sulfuric acid.

GAINESVILLE, FLA.

(14) Melting points are uncorrected. Analyses are by the Peninsular ChemResearch, Inc., Gainesville, Fla.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Hydrolysis of Certain ζ-Ketonitriles

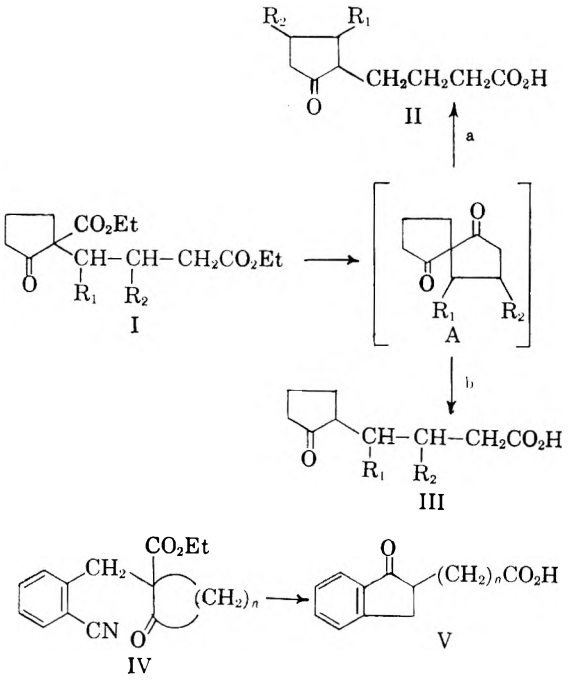
WERNER HERZ

Received November 7, 1956

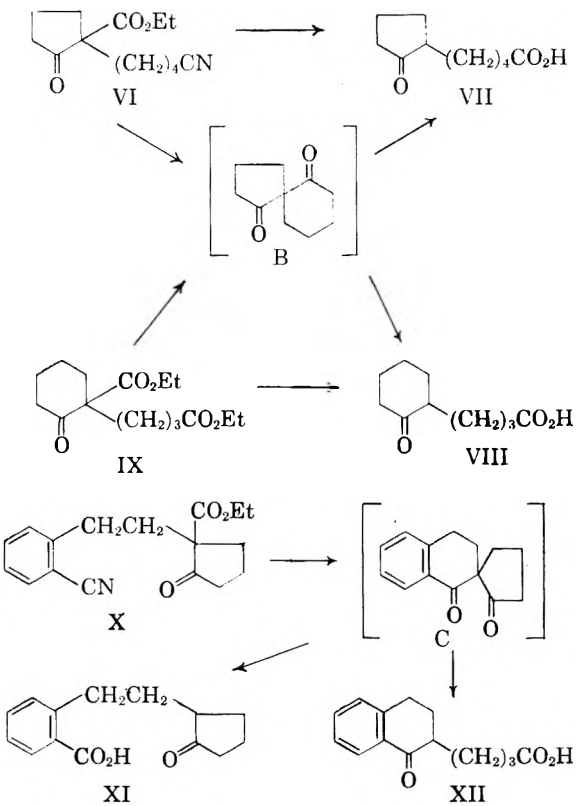
In contrast with their lower homologs, 5-(1-carbethoxy-2-oxocyclopentyl)valeronitrile and ethyl 2-keto-1-[β-(*o*-cyanophenyl)ethyl]cyclopentane carboxylate are hydrolyzed and decarboxylated by hydrochloric acid without rearrangement.

Earlier papers of this series[1,2] demonstrated that β-ketoesters of type I and IV on acid hydrolysis undergo rearrangement and furnish ε-ketoacids of type II and V respectively. The spirodiketone A was suggested as a possible intermediate for the first series of isomerizations; analogous diketones may be postulated for other such rearrangements.[3]

At first glance there appears to be no simple explanation for the implied assumption that the diketone A is cleaved preferentially by path *a* instead of *b*, unless the reaction is equilibrium rather than rate-controlled.[4] One must then ask why II should be favored over III. In the case of the aromatic ε-ketoacids obtained from IV, the increased stabilization which results when the carbonyl group is conjugated with the aromatic ring may conceivably be invoked as furnishing the driving force for the rearrangement.



In order to gain more information on the extent of the rearrangement it was decided to investigate the acid-catalyzed hydrolysis of two potential ζ-ketoacids, VI and X.[6] If the spirodiketones B and C are capable of formation under the conditions of the reaction, the possibility of isomerization is clearly indicated.



The results show that no rearrangement occurs when VI and X are refluxed with concentrated hydrochloric acid. The solid acid obtained by hydrolysis of VI melted at a temperature which corresponded to the melting point of the rearrangement product, 4-(2-oxocyclohexyl)butyric acid (VIII), but its infrared spectrum, a mixed melting point determination and the melting points of several derivatives clearly differentiated it from VIII and established its structure as VII. This was confirmed

(1) W. Herz, *J. Am. Chem. Soc.*, **78**, 1485 (1956).
(2) W. Herz, *J. Am. Chem. Soc.*, **78**, 2529 (1956).
(3) F. Ramirez and A. P. Paul, *J. Am. Chem. Soc.*, **77**, 1035 (1955).
(4) But the alcoholysis of certain 1,3-diketones in the presence of hydrogen chloride which corresponds to the cleavage step above does not appear to be reversible.[5]
(5) H. Adkins, W. M. Kutz, and D. D. Coffman, *J. Am. Chem. Soc.*, **52**, 3212 (1930).
(6) The choice of these compounds was dictated by the relative ease of preparation as well as by the hope that any tendency to form the postulated intermediates (the spirodiketones or their imino analogs) would be enhanced if the carbethoxy group were replaced by the cyanide radical.

by Wolff-Kishner reduction of VII to the known 5-cyclopentylvaleric acid.

The structure of VIII would seem to be well authenticated since it has been prepared by three different methods.[7–9] In the course of the present work it was also prepared by acid hydrolysis of IX. This indicates that the spirodiketone B is not in equilibrium with VII or VIII under the conditions used since otherwise the same compound, or mixture of compounds, should have been obtained from VI *and* from IX.

The β-ketoester X was prepared in low yield by condensation of cyclopentanone carboxylic ester with β-*o*-cyanophenylethyl bromide which in turn was obtained from *o*-cyanohydrocinnamic acid by the Hunsdiecker reaction. Hydrolysis of X with concentrated hydrochloric acid resulted, as in an earlier instance,[2] in two products. The neutral fraction was identified as the nitrile corresponding to XI. The acidic fraction, a viscous oil, was not identical with 1-tetralone-2-butyric acid, m.p. 64–65°;[10] its infrared spectrum and the ultraviolet spectrum of its dinitrophenylhydrazone showed that the ketone group was not conjugated. The structure of the ketoacid must therefore be represented as XI which demonstrates that hydrolysis of X was not accompanied by rearrangement.

EXPERIMENTAL[11]

δ-(1-Carbethoxy-2-oxocyclopentyl)valeronitrile. To a suspension of 11.5 g. of powdered sodium in 400 ml. of toluene was added with heating and stirring 78 g. of ethyl cyclopentanone-2-carboxylate. After 2 hr. at reflux 81 g. of δ-bromovaleronitrile was added in one portion. The mixture was refluxed and stirred for an additional 18 hr., cooled, diluted with water and acidified with a little acetic acid. The toluene layer was separated and washed, dried and distilled. After a relatively large forerun containing starting material (mixture of nitrile and ester), the product was collected at 166–174° (2 mm.), wt. 43 g. (39%). The analytical sample boiled at 151–152° (0.5 mm.), n_D^{24} 1.4656.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.37; H, 8.17; N, 5.94.

The semicarbazone, recrystallized several times from ethanol, melted at 154–156°.

Anal. Calcd. for $C_{14}H_{22}N_4O_3$: C, 57.12; H, 7.53. Found: C, 57.37; H, 7.51.

δ-(2-Oxocyclopentyl)valeric acid. A mixture of 40 g. of the preceding ester and 200 ml. of concentrated hydrochloric acid was refluxed for 20 hr., cooled, made basic, and extracted with ether. The aqueous layer was acidified and extracted with ether and the ether layer was dried and distilled. The product boiled at 163–168° (1.5 mm.), wt. 10.8 g. (35%). There was a considerable amount of high-boiling residue. The product crystallized on standing. After recrystallization from benzene-ligroin (b.p. 65–110°) it melted at 57–58°. The melting point of 4-(2-oxocyclohexyl)butyric acid is variously given as 57–58°,[7] 60–61°[8] and 56–57.5°.[9] The infrared spectrum, however, indicated that the compound was a cyclopentanone derivative (strong split carbonyl band with peaks at 1730 (cyclopentanone) and 1710 (carboxyl), and the derivatives melted generally higher than the corresponding derivatives of the cyclohexanone.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.62.

The *semicarbazone* was recrystallized from ethanol in which it was rather insoluble, m.p. (capillary) 195–196° (dec.) with previous darkening, m.p. (Kofler) 207–208°.

Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.84; H, 7.65; N, 16.9.

The *oxime* was recrystallized from ethanol-water and melted at 124–125.5.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.79; H, 8.20; N, 6.64.

The *p-phenylphenacyl ester* was recrystallized from ethanol-water by taking up in a small amount of hot ethanol, allowing to cool, adding water to incipient cloudiness, adding a few drops of ethanol until the cloudiness had disappeared and allowing to stand. The colorless crystals melted at 71–72°.

Anal. Calcd. for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 76.37; H, 6.61.

δ-Cyclopentylvaleric acid. Reduction of 4 g. of the ketoacid by the procedure of Huang-Minlon[12] furnished 3.1 g. of an acid, b.p. 125–130° (2 mm.) [lit. 150–153 (9 mm.),[13] 149–150° (9 mm.)[14]], m.p. 9–10° (lit. 11°,[13] 12.5–14°[14], 14–15°[14]). The amide melted at 134–135° (lit. 138°,[13] 135–136°.[14]). The anilide melted at 78–79°, lit. 81°.[13] Mixed melting points with derivatives of authentic material prepared by the method of Coleman and coworkers[14] showed no depression.

Ethyl 4-(1-carbethoxy-2-oxocyclohexyl)crotonate. A suspension of 8.2 g. of potassium in 300 ml. of dry toluene was treated with 36 g. of cyclohexanone carboxylic ester and refluxed, with stirring, for 3 hr. A solution of 41 g. of ethyl γ-bromocrotonate in 50 ml. of toluene was then added dropwise. After 20 hr. at reflux, the mixture was worked up in the usual way and distilled, b.p. 166–174° (2.5 mm.), wt. 17.5 g. There was a considerable amount of high-boiling residue. The analytical specimen, b.p. 170–172° (2.5 mm.), n_D^{24} 1.4788, exhibited bands at 1730 and 1660 cm.$^{-1}$ in the double bond region of the infrared spectrum.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.29; H, 8.02.

The *semicarbazone* was recrystallized from ethanol-water (2:3) by seeding at room temperature and allowing to stand, m.p. 117–119°.

Anal. Calcd. for $C_{16}H_{25}O_5N_3$: C, 56.62; H, 7.43; N, 12.4. Found: C, 56.96; H, 7.59; N, 12.2.

Ethyl 4-(1-carbethoxy-2-oxocyclohexyl)butyrate. A solution of 14.5 g. of the unsaturated ester in 100 ml. of absolute ethanol was hydrogenated at 3 atm. (catalyst 5% palladium-on-charcoal) until hydrogen uptake ceased. The product was collected at 145–155° (1.5 mm.), wt. 11.2 g. The analytical sample boiled at 150–152° (1.5 mm.), n_D^{23} 1.4628.

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.75; H, 8.58.

(7) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937).

(8) W. Hückel and H. Naab, *Ann.*, **502**, 151 (1933).

(9) I. H. Nazarov and M. S. Burmistrova, *Zhur. Obshchei Khim.*, **20**, 1304 (1950).

(10) G. D. Johnson, W. B. Lindsey and B. R. Jones, *J. Am. Chem. Soc.*, **78**, 461 (1956). I am indebted to Dr. G. D. Johnson for furnishing me with an authentic sample of this compound.

(11) Melting and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were run by Miss Martha Brackett and Mr. Joseph Kovacic on a Perkin-Elmer Model 21 double beam instrument. Ultraviolet spectra were determined by Mrs. Shirley Ann Pinner and Dr. Enrico Clementi on a Beckman Model DK 1 recording spectrophotometer.

(12) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(13) M. M. Katsnelson and M. S. Kondakova, *Compt. rend. acad. sci., URSS*, **17**, 367 (1937); *Chem. Abstr.* **32**, 7022 (1938).

(14) G. H. Coleman, J. E. Callen and C. A. Dornfeld, *J. Am. Chem. Soc.*, **68**, 1101 (1946).

The *semicarbazone*, m.p. 114–114.5°, was recrystallized from benzene-ligroin (b.p. 65–110°).

Anal. Calcd. for $C_{16}H_{27}N_3O_5$: C, 56.29; H, 7.97; N, 12.3. Found: C, 56.42; H, 7.72; H, 12.3.

4-(2-Oxocyclohexyl)butyric Acid. A mixture of 9.3 g. of the preceding ester and 75 ml. of concentrated hydrochloric acid was refluxed for 18 hr., cooled, made basic, extracted with ether, acidified, and again extracted with ether. The ether extract containing the acid fraction was dried and distilled; yield 4.1 g., b.p. 165–175° (3 mm.). The product solidified on standing and was recrystallized from petroleum ether (b.p. 30–60°) furnishing crystals of m.p. 57.5–59.5°, mixed m.p. with 5-(2-oxocyclopentyl)valeric acid 40–48°. The semicarbazone melted at 186–187° (lit. 185,[7] 189°,[8] 187–188°[9]). The oxime melted at 101–103° (lit. 101–103°,[8] 102–104°[7]). This ketoacid had only one strong band in the double bond region of the infrared spectrum (1710 cm.$^{-1}$, combination of carboxyl and cyclohexanone carbonyl).

β-o-Cyanophenylethyl bromide. *o*-Cyanocinnamic acid[15] was reduced catalytically (solvent absolute ethanol, catalyst 5% palladium-charcoal) to *o*-cyanodihydrocinnamic acid in 85–90% yield. The latter (16 g.) was converted to the silver salt by dissolving in the calculated amount of 1% sodium hydroxide solution and mixing with 170 g. (10% excess) of 10% silver nitrate solution. The precipitate was filtered, washed thoroughly with distilled water, ethanol, acetone, and ether, dried in a vacuum oven at 60° for one week and stored over phosphorus pentoxide; yield 23.5 g. (89%). The salt, wt. 40 g., was suspended in 150 ml. of dry carbon tetrachloride in a vessel protected from atmospheric moisture and a solution of 24 g. of dry bromine in 60 ml. of carbon tetrachloride was added with stirring and heating on the steam bath in the course of 3 hr. Stirring and heating was continued for an additional 4 hr. The mixture was cooled, filtered, washed with sodium bicarbonate solution, dried, and distilled; b.p. 111–116 (2 mm.), n_D^{23} 1.5719. The yields from several runs averaged 10 g. (34%); the bicarbonate washings yielded 1–3 g. of starting material.

Anal. Calcd. for C_9H_8BrN: C, 51.40; H, 3.84; N, 6.67. Found: C, 51.65; H, 3.92; N, 6.90.

Ethyl 2-keto-1-[β-(o-cyanophenyl)ethyl]cyclopentane carboxylate. To a suspension of 4.2 g. of potassium in 150 ml. of dry toluene was added 23.4 g. of cyclopentanonecarboxylic ester. After 5 hr. of stirring and heating a solution of 21 g. of *β-o*-cyanophenylethyl bromide in 75 ml. of toluene was added. Stirring and refluxing was continued for 3 days. The cooled mixture was diluted with water, acidified with acetic acid, the toluene layer washed with water, the aqueous washings were washed with ether, and the combined organic layers dried. The ether was removed and the residue was distilled in a short-path still. The first fraction, b.p. 75–120° (2 mm.), wt. 12.5 g. consisted primarily of cyclopentanonecarboxylic ester; the product, wt. 8.5 g. (30%), boiled unsharply in the range 190–195° because of pressure fluctuations arising from decomposition. Redistillation gave a colorless liquid, b.p. 180–185° (2 mm.), infrared bands at 2330 (CN) and 1730 cm.$^{-1}$ (shoulder at 1755 cm.$^{-1}$).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.9. Found: C, 71.51; H, 6.65; N, 5.0.

The *semicarbazone* melted at 186.5–188° after three recrystallizations from aqueous ethanol.

Anal. Calcd. for $C_{18}H_{22}O_3N_4$: C, 63.14; H, 6.45; N, 16.4. Found: C, 62.95; H, 6.45; N, 16.4.

The above run represented the best of several similar condensations the yields from which varied widely but never exceeded 30%. Decomposition during the distillation was undoubtedly a factor, but the major reason for the low yields appeared to be dehydrohalogenation of the bromide under the influence of base. Thus an attempt to condense *o*-cyanophenylethyl bromide with the sodium derivative of cyclohexanonecarboxylic ester in *t*-butyl alcohol, a method which has been recommended for condensations with other phenylethyl bromides,[16,17] resulted in the isolation of a large fraction of b.p. 75–85° (2 mm.), which was a mixture of cyclohexanonecarboxylic ester and *o*-cyanostyrene (polymer formation on standing) as well as some high-boiling material which distilled over a wide range.

The condensation of *o*-cyanophenylethyl bromide with diethyl benzylmalonate was also investigated as the initial step in another projected synthesis. In addition to a 60% recovery of benzylmalonic ester and high-boiling residue, there was obtained a 55% yield of *o*-cyanostyrene, b.p. 95–102° (9 mm.), identified as the dibromide, m.p. 84.5–85.5° (lit. 86–86.5[18]).

2-β-(o-Cyanophenyl)ethylcyclopentanone. A mixture of 6.5 g. of the preceding β-ketoester and 30 g. of concentrated hydrochloric acid was refluxed for 12 hr., cooled, made basic, extracted with ether, acidified, and again extracted with ether. The neutral fraction was distilled to yield 2.4 g., b.p. 155–160° (2 mm.). The infrared spectrum had bands at 2230 (CN) and 1740 cm.$^{-1}$ (cyclopentanone).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.59. Found: C, 78.94; H, 7.18; N, 6.80.

The *semicarbazone* was recrystallized from ethanol and melted at 204–205° (dec. slowly above 200°).

Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.66; H, 6.71. Found: C, 66.36; H, 6.39.

The *2,4-dinitrophenylhydrazone*, orange-yellow crystals, (λ max 364 mμ), m.p. 151.5°, was recrystallized from benzene.

Anal. Calcd. for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.8. Found: C, 60.93; H, 4.94; N, 17.8.

2-β-(o-Carboxyphenyl)ethylcyclopentanone. The acid fraction from the preceding hydrolysis, crude wt. 1.8 g., could not be crystallized. It was distilled in a sublimator at a bath temperature of 190° (0.5 mm.). The infrared spectrum had bands at 1725 (cyclopentanone), 1695 (conjugated carboxyl) and 1408 cm.$^{-1}$ (—CH_2—C(=O)—) and differed considerably from the infrared spectrum of 1-tetralone-2-butyric acid, m.p. 64–65°, the possible rearrangement product which had bands at 1708 (carboxyl) and 1680 cm.$^{-1}$ (1-tetralone).

The analysis of the oil was low in carbon, but conversion to the 2,4-dinitrophenylhydrazone resulted in a satisfactory derivative.

The dinitrophenylhydrazone was chromatographed over alumina (solvent ethyl acetate). Ethyl acetate eluted a small amount of a yellow impurity; the major fraction was developed with 95% ethanol and eluted with 95% ethanol containing 2% acetic acid. Recrystallization from ethanol furnished golden-yellow needles m.p. 199–200° (dec.), whose ultraviolet spectrum (λ_{max} 364 mμ) showed that they were not derived from a conjugated ketone.

Anal. Calcd. for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.28; H, 4.79; N, 13.20.

Acknowledgment. This work was supported by grants from the Research Council of the Florida State University and from the National Science Foundation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MOUNT ALLISON UNIVERSITY]

Tertiarybutylbenzenes. IV. Mechanism of Friedel-Crafts Cyclialkylations with *tert*-Butyl Chloride. Comparative Alkylations with 2-Chloro-2,5-dimethylhexane

L. ROSS C. BARCLAY AND JOHN W. HILCHIE

Received December 26, 1956

Friedel-Crafts alkylations of *p*-di-*tert*-butylbenzene and of benzene with 2-chloro-2,5-dimethylhexane produced 1,1,4,4,-5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydroanthracene (I). The significance of this finding relative to the mechanism of formation of (I) from alkylations using *tert*-butyl chloride is discussed.

An earlier communication[1] reported the formation of 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydroanthracene (I) from the alkylation of 1,3,5-tri-*tert*-butylbenzene or *p*-di-*tert*-butylbenzene with *tert*-butyl chloride. A mechanism for this unusual cyclialkylation was proposed which involved the formation of isobutane and a tri-*tert*-butylbenzenecarbonium ion (II). It was suggested that a six-membered ring formed from the latter by addition and cyclialkylation involving isobutylene.

There are two inherent objections to this proposed mechanism. In the first place it involves a high energy primary carbonium ion, and secondly this neophyl cation (II) would be expected to rearrange readily to the more stable tertiary carbonium ion (III) before taking up isobutylene. Then subsequent cyclialkylation of (III) with isobutylene would lead to isomers of octamethyloctahydroanthracene other than (I). Lien and MacCaulay[2] have postulated the rearrangement of a carbonium ion such as (II) to account for the formation of β-alkylstyrenes when *tert*-butylbenzene is treated with hydrogen fluoride and boron trifluoride. This result is illustrated by the equations B.

In view of these objections, a more plausible explanation for these cyclialkylations can be derived from the recent results of Condon[3] who discovered that on contact with aluminum chloride *tert*-butyl chloride produces a small yield of 2,5-dichloro-2,5-dimethylhexane. This result is summarized by the equations C.

The 2,5-dimethyl-2-hexyl carbonium ion (IV) provides the required carbon skeleton for the production of (I). The present experiments prove the ability of the ion (IV) to replace the *tert*-butyl groups on the aromatic nucleus and then cyclize to form the required six-membered ring. *p*-Di-*tert*-butylbenzene is thus converted in good yield into (I) most probably by the scheme shown by the equations D. This scheme also accounts for the formation of isobutane which was detected in earlier experiments.[1]

This mechanism requires a rather congested transition state with two tertiary alkyls *ortho* to each other on the aromatic nucleus. Proton migrations to *ortho* positions are also implied. A reasonable alternative would be to suppose that a 2,5-dimethyl-2-hexyl cation will directly displace a *tert*-butyl cation, thus producing *p*-(2,5-dimethyl-2-hexyl)-*tert*-butylbenzene as the first intermediate. Our experiments cannot distinguish between these two alternatives. It would appear to be necessary to use both schemes to account for the formation of (I) from 1,3,5-tri-*tert*-butylbenzene.

Benzene could not be cyclialkylated with 2-chloro-2,5-dimethylhexane under similar conditions to those which produced (I) with 2,5-dichloro-2,5-dimethylhexane.[1] However, when two moles of aluminum chloride per mole of benzene were used under the special conditions of these experiments, a 10% yield of (I) was obtained.

In this case the cyclization of (V) requires a carbonium ion at position 5 of the 2,5-dimethyl-2-hexyl side chain. To accomplish this, it is conceivable that a hydride ion could be transferred to a proton and be expelled as hydrogen or it could undergo exchange with the chlorine of another molecule of 2-chloro-2,5-dimethylhexane. The latter seems more reasonable and accounts for the low yield of (I).

Before Bartlett's[4] identification of 1,3,5-tri-*tert*-butylbenzene (m.p. 72.5–73.0°), a compound of m.p. 128° had been reported at various times in the literature as tri-*tert*-butylbenzene[5] and as 1,2,4-tri-*tert*-butylbenzene.[6] This compound has also been reexamined by Bartlett. The structure suggested above seems most unlikely since Brown[7] has shown that it is highly improbable that two *tert*-butyl groups can occupy adjacent positions in the benzene ring. In the light of the present work, it would

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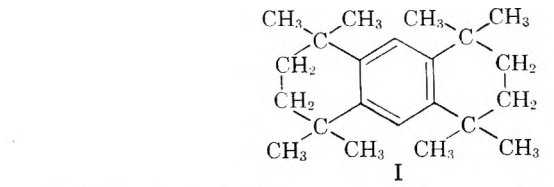
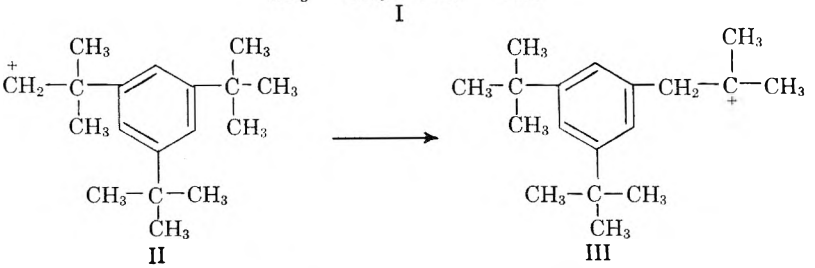


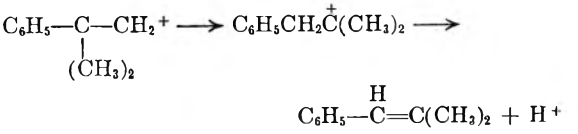
I

A



II III

B



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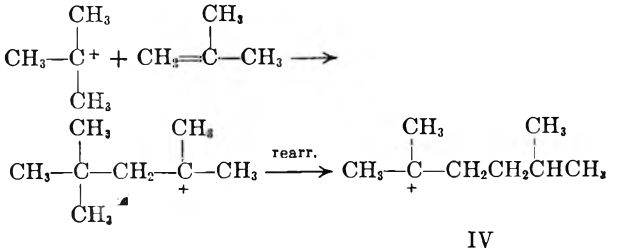
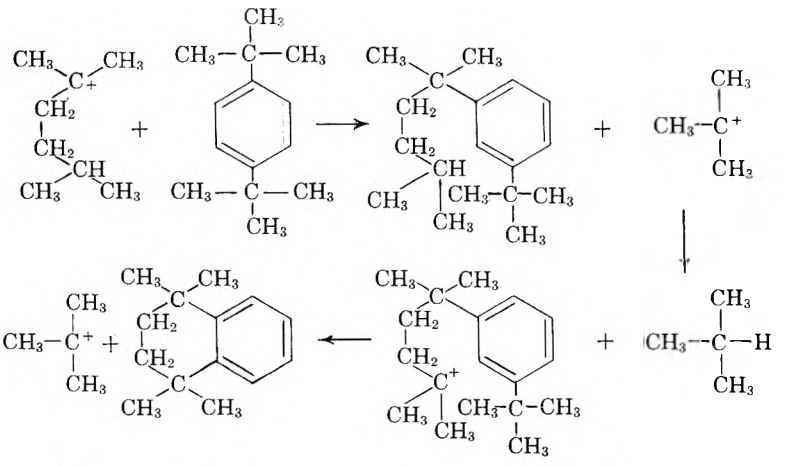


IV

D



V VI

appear that a reasonable structure for this compound would be (VI). This compound would be practically indistinguishable from tri-*tert*-butylbenzene in the ultimate analyses. Experiments are presently being conducted to test this suggestion.

EXPERIMENTAL

Ultraviolet spectra were recorded on a Beckmann DU Spectrophotometer in cyclohexane. Melting points were done on a Fisher-Johns apparatus and are uncorrected.

2,5-Dimethyl-2-hexanol. A Grignard reagent was prepared from 127 g. (0.84 mole) of freshly distilled isoamyl bromide and 20 g. (0.84 mole) of magnesium. To this reagent was added dropwise 49 g. (0.84 mole) of acetone in an equal volume of anhydrous ether. After the initial vigorous reaction the reaction mixture was left overnight. The product was decomposed with ice and then poured into 10% sulfuric acid and the organic layer separated and dried over anhydrous sodium sulfate. After removal of the ether on the

steam cone, the residue was fractionated in a Podbielniak-type column. A yield of 30 g. of the alcohol distilling at 152–155°, $n_D^{11.4}$ 1.4250 (lit.,[1] b.p. 152–154°, $n_D^{11.4}$ 1.42428) was obtained.

2-Chloro-2,5-dimethylhexane. 2,5-Dimethyl-2-hexanol (13 g., 0.10 mole) was shaken intermittently with 42 ml. of concentrated hydrochloric acid over a 1-hr. period. Fresh acid was charged into the separatory funnel and this process was repeated. The organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure. The yield of 2-chloro-2,5-dimethylhexane, b.p.$_{20\ mm.}$ 58°, n_D^{15} 1.4255; (lit.,[8] b.p.$_{14\ mm.}$ 44–45°, n_D^{15} 1.42495) amounted to approximately 50%.

Alkylations. (1) p-Di-tert-butylbenzene. A solution of 2-chloro-2,5-dimethylhexane (3 g., 0.02 mole) and *p*-di-*tert*-butylbenzene (1.90 g., 0.01 mole) in 5 ml. of carbon bisulfide was cooled below 0° in an ice salt bath. Powdered anhydrous aluminum chloride (2.66 g., 0.02 mole) was added in small portions to the stirred reaction mixture over a period of 2 hr. During this time there was copious evolution of hydrogen chloride and a brown complex formed at the bottom of the reaction mixture. After a total of 4 hr. reaction time, the complex was decomposed in water and allowed to stand overnight. The semisolid organic layer was extracted with ether and the ether solution concentrated to yield colorless needles, 1.20 g., yield 40%. This product softened above 200° and melted at 220°. A sample recrystallized from ethanol-benzene proved to be identical (by mixed melting point and ultraviolet spectra) to the octahydrooctamethylanthracene (m.p. 220°) reported earlier.

(2) Benzene. A mixture of benzene (3.1 g.) and 2-chloro-2,5-dimethylhexane (3.0 g.) was treated with catalytic amounts of anhydrous aluminum chloride (0.1 g.) below 0°. No observable reaction took place in the cold. The reaction mixture was then left at room temperature for two days. However, working up of the product yielded only volatile liquids and no trace of solid hydrocarbon.

In a second experiment a mixture of 2-chloro-2,5-dimethylhexane (3.0 g., 0.02 mole) and benzene (0.78 g., 0.01 mole) was cooled below 0°. Anhydrous aluminum chloride (2.66 g., 0.02 mole) was added in small portions over a 3-hr. period to the reaction mixture kept below 0°. After about 3 hr. reaction time a few milliliters of carbon bisulfide was added to facilitate stirring of the semisolid mass. The reaction was continued for a total of 8 hr. after which time the temperature had risen to 20°. The complex was decomposed in water and after standing overnight a crystalline crust formed in the hydrocarbon layer. Extraction with ether and concentration of the ether yielded 0.31 g. of colorless needles. This product proved to be identical with octamethyloctahydroanthracene by mixed melting point and ultraviolet spectrum.

(8) *Beilstein*, I, 422.

Acknowledgments. The authors express their thanks to the National Research Council of Canada for financial assistance. We are indebted to G. A. Harrington of the Indoil Chemical Company, Chicago, for a generous sample of *p*-di-*tert*-butylbenzene.

SACKVILLE, N. B.
CANADA

[CONTRIBUTION FROM E. I. DU PONT DE NEMOURS & CO., INC., EASTERN LABORATORY]

Reaction of Nitric Oxide with Nitrosocyclohexane Dimer

L. G. DONARUMA AND D. J. CARMODY

Received October 29, 1956

The reaction of nitric oxide with bisnitrosocyclohexane has been studied. The possibility that an adduct of nitric oxide with the nitroso compound is formed and rearranges to cyclohexyldiazonium nitrate is discussed. A rationalization for the formation of the products, cyclohexyl nitrate, cyclohexyl nitrite, and nitrocyclohexane, by decomposition of the diazo nitrate is presented.

The reaction of nitric oxide with hydrocarbons (I) has been studied by other investigators.[1] The major products of this reaction are the nitrate (II), the nitroparaffin (III), and the nitrite (IV). We have studied the reaction of nitric oxide with cyclo-

$$\underset{(I)}{RH} \xrightarrow[NO]{\Delta} \underset{(II)}{RONO_2} + \underset{(III)}{RNO_2} + \underset{(IV)}{RONO}$$

(Subscript "a" indicates that R = cyclohexyl.)

hexane in the presence of various dehydrogenation catalysts and obtained similar products.

$$I_a \xrightarrow[NO]{\Delta\ Catalyst} II_a + III_a + IV_a + C_6H_{11}OH + \text{traces of nitroolefins and carbonyl compounds}$$

Catalyst = Pt, Pd, S, NO_2

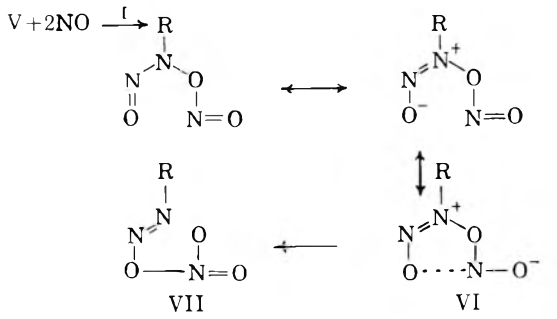
(1) Burkhard, Brown, Herrick, Myers, and Hurd, paper presented at the 126th Meeting, American Chemical Society, New York, N. Y., September 1954.

Brown[2] suggested that nitroso compounds (V) are intermediates in the reaction of nitric oxide with hydrocarbons. We allowed nitrosocyclohexane to react (V_a) with nitric oxide and obtained cyclohexyl nitrate (II_a), nitrocyclohexane (III_a), and cyclohexyl nitrite (IV_a) as the major products. Brown[2] suggested that diazo nitrates (VII) are formed by the reaction of nitric oxide with nitroso compounds (V) and that the isolable products are formed by the decomposition of the diazo nitrate followed by reaction of the decomposition products with oxides of nitrogen present in the reaction mixture.[2,3]

$$\underset{V_a}{1/2(C_6H_{11}NO)_2} \rightarrow C_6H_{11}NO \xrightarrow[1\text{–}6\ atm.]{NO,\ 25°\text{–}50°} II_a + III_a + IV_a + \text{traces of carbonyl compounds and other nitrated products}$$

(2) Brown, paper presented at the 126th Meeting, American Chemical Society, New York, N. Y., September 1954.

(3) Gray and Yoffe, *Quart. Revs.*, 362 (1955).



VII VI

$$VII \longrightarrow R\cdot + N_2 + \cdot NO_3$$
$$\hookrightarrow R^+ + N_2 + {}^-NO_3$$

$$R\cdot + I + \cdot NO_3 \longrightarrow RONO_2^* \xrightarrow{I} RONO_2 + I^*$$
$$R^+ + {}^-NO_3 \longrightarrow RONO_2$$
$$RO\cdot + \cdot NO_2 \longrightarrow RONO_2$$
$$\cdot NO_3 + \cdot NO \longrightarrow 2\cdot NO_2$$
$$R\cdot + \cdot NO_2 \longrightarrow RNO_2^* + RONO^* \xrightarrow{I} RNO_2 + RONO + I^*$$
$$RONO^* \longrightarrow RO\cdot + \cdot NO$$
$$I^* \xrightarrow[\text{or wall}]{\text{solvent (I)}} I$$

In order to investigate the reaction further, a study was made of the rate of reaction of nitrosocyclohexane with nitric oxide in cyclohexane solution at temperatures of 25°–51° and pressures of 0.5–6 atmospheres. Table I shows the results of the kinetic measurements.

TABLE I

REACTION OF BISNITROSOCYCLOHEXANE WITH NITRIC OXIDE AT VARIOUS TEMPERATURES AND PRESSURES IN CYCLOHEXANE

T°C.	Pressure (p.s.i. ga.)	10^3k (min.$^{-1}$)	ΔS‡ (e.u.)
25°	21.5	1.15	—
25°	69	1.17	—
25°	50	1.14	77.9
33.5°	50	10.4	77.9
51°	50	462.	76.9

E_A = 47,700 cal./mole
ΔH‡ = 47,085 cal./mole

The rate constants indicate that the rate may be independent of nitric oxide pressure. Even at pressures as low as 0.5 atmospheres the rate did not drop off.[4] At the low pressures, the rate constants drifted somewhat during the initial stages of the reaction. This may have been due to diffusion effects.

When nitric oxide was admitted to a solution of bisnitrosocyclohexane in cyclohexane, a temperature rise occurred. This observation and the apparent zero order dependence of the rate on nitric oxide suggested that perhaps nitric oxide was reacting initially with nitrosocyclohexane to form a complex of some nature. Figure 1 shows the infrared

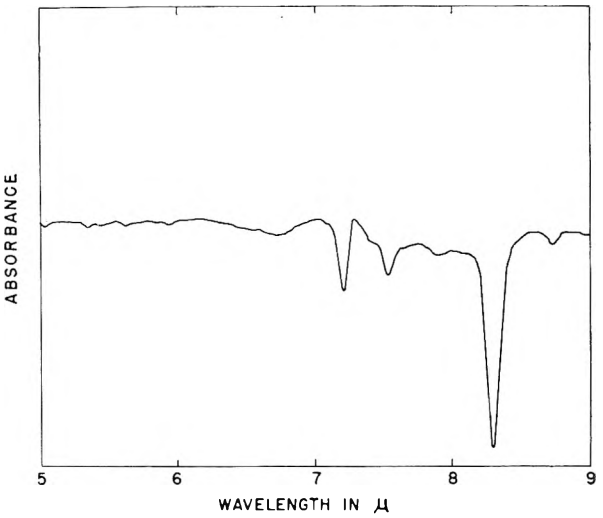


FIG. 1.—INFRARED SPECTRUM OF A CYCLOHEXANE SOLUTION OF BISNITROSOCYCLOHEXANE

spectrum of bisnitrosocyclohexane in cyclohexane (concentration 0.1 g./100 ml.). Infrared spectra also were taken of cyclohexane solutions of bisnitrosocyclohexane which had been in contact with nitric oxide (Figure 2). Figure 2 shows that the

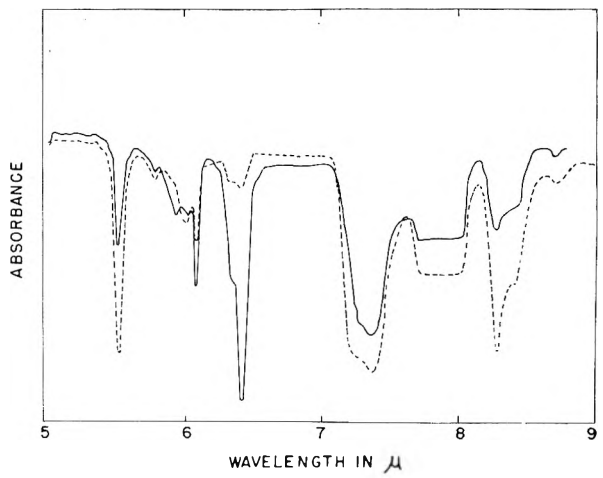


FIG. 2.—INFRARED SPECTRA OF A CYCLOHEXANE SOLUTION OF NITRIC OXIDE AND NITROSOCYCLOHEXANE

usual nitroso band at 8.28 μ has broadened and been modified by the contact with nitric oxide, a new band has appeared at 5.5 μ, and at 6.10 μ and 6.44 μ where the nitrate and nitro bands, respectively, appear, the products are beginning to form (dotted line

(4) Actually, rate measurements were made at pressures as low as 20 mm. ga. in an apparatus consisting of a gas filled nitrometer tube connected to a sealed reaction flask. Agitation was supplied with a magnetic stirrer. The reactions in this apparatus were run over shorter periods of time at higher bisnitrosocyclohexane concentrations (0.1 g./100 ml.). The rates were affected by diffusion during the initial stages of the reaction. However, after contact with nitric oxide for 1 hr., the reaction rate constants were never smaller than those obtained at higher pressures. For example, the rate constant obtained at 25° and 20 mm. ga. pressure over a period of 1 hr. was 1.32×10^{-3} (min.$^{-1}$). Constant pressure over longer periods of time could not be maintained in the apparatus. Checks at 0.5 atm. ga. in the shaker gave similar results.

spectrum). Furthermore, it can also be seen that upon standing (solid line spectrum), the intensity of the modified nitroso band at 8.28 μ diminished and the intensities of the nitrate and nitro bands increased. The new band at 5.5 μ also exhibits similar behavior. Figure 3 shows that the spectrum of bis-

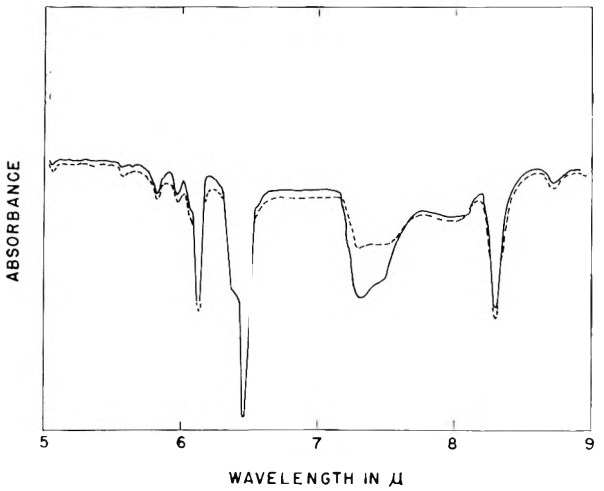
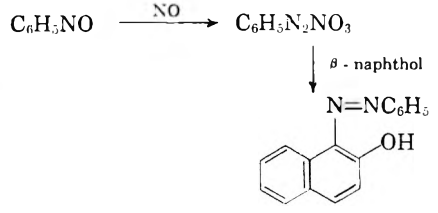


FIG. 3.—INFRARED SPECTRA OF A WATER WASHED CYCLOHEXANE SOLUTION OF NITRIC OXIDE AND NITROSOCYCLOHEXANE.

nitrosocyclohexane at 8.28 μ returned to its usual shape (Figure 1) after washing with water to regenerate bisnitrosocyclohexane from the complex, and that the intensities of the nitro and nitrate bands were not affected by the water wash. Since nitric oxide is very insoluble in cyclohexane at atmospheric pressure and no bands characteristic of nitric oxide[5] appear in the spectra in Figure 2, the spectral data might be interpreted as indicating that a complex is formed from nitric oxide and nitrosocyclohexane.

The high positive entropy of activation shown in Table I was interpreted to indicate that any transitory species formed by the action of nitric oxide on nitrosocyclohexane has a greater number of degrees of freedom than the initial reactants.[6] If a complex such as VI_a was formed by reaction of nitric oxide with nitrosocyclohexane, the complex (VI_a) should isomerize to the diazo nitrate (VII_a) if the postulated mechanism is creditable. To do this, the binding forces in the complex should weaken and the resulting loosening of the structure should be accompanied by a large increase in entropy.[6] Such changes in the structure of an activated state should give a large entropy of activation as was found experimentally. Moreover, the high entropy increase can help compensate for the high activation energy. The rapid reaction rates observed, despite the high activation energy, at the moderately low temperatures employed in this study are consistent with a large entropy increase.[6] Such a relationship of reaction rate to activation entropy is well known in the denaturation of proteins.[6]

Positive entropies of activation also are characteristic of reactions which yield several products from a single species[6] and if a diazo nitrate (VII_a) is an intermediate in the reaction and does decompose to yield a nitrate (II_a), a nitroparaffin (III_a), and a nitrite, the presence of a diazonium nitrate as an intermediate would be expected to contribute markedly to a high positive activation entropy. Moreover, Bamberger[7,8] has shown that nitrosobenzene reacts with nitric oxide to yield benzene diazonium nitrate.



These observations and the fact that Brown[2] found that nitrogen was the only gas formed in the reaction of hydrocarbons with nitric oxide make it appear possible that a diazo nitrate is an intermediate in this reaction. It seems likely that the changed spectrum (Figure 2) of the nitroso compound (V_a) after exposure to nitric oxide is not characteristic of a diazonium nitrate. Diazonium salts absorb strongly at 4.3–4.7 μ.[9] No absorption was noticeable in this region of the spectrum.

The kinetic data, the spectral data, and the work of Brown[2] and Bamberger[7,8] indicate that the reaction of nitric oxide with nitrosocyclohexane might involve the rapid formation of an adduct (VI_a) of nitric oxide with all or most of the nitroso compound (V_a). This adduct may or may not have the structure (VI_a) which Brown has postulated. The adduct might then rearrange to cyclohexyldiazonium nitrate (VII_a) and decompose homolytically and/or heterolytically to yield species which can react with oxides of nitrogen present in the system to yield cyclohexyl nitrate (II_a), nitrocyclohexane (III_a), and cyclohexyl nitrite (IV_a).

$$V_a + 2NO \longrightarrow VI_a \longrightarrow VII_a \longrightarrow II_a + III_a + IV_a + N_2$$

The apparent zero order of the reaction in nitric oxide and the temperature rise upon the addition of nitric oxide to the system make it seem likely that the formation of the complex (VI_a) is fairly rapid and complete with little or no tendency of the complex (VI_a) to revert back to nitric oxide and nitrosocyclohexane (V_a). Stable aliphatic diazonium salts appear to be unknown. Therefore, it would be expected that if a diazo nitrate (VII_a) were formed

(5) Pearson, Fletcher, and Gantz, *Anal. Chem.*, **28**, 1218 (1956).

(6) Glasstone, Laidler, and Eyring, *The Theory of Rate Processes*, pp. 21–27, 196, 296, 407, 442–446. McGraw-Hill, Inc., New York, 1941.

(7) Bamberger, *Ber.*, **51**, 634 (1918).

(8) Bamberger, *Ber.*, **30**, 508 (1897).

(9) Whetsel, Hawkins, and Johnson, *J. Am. Chem. Soc.*, **78**, 3360 (1956).

in the reaction it would decompose rapidly to yield the observed reaction products (II_a, III_a, IV_a). The dissociation of bisnitrosocyclohexane (V_a) to the monomeric state must also be a fast change because of the observed nitric oxide order. This line of reasoning seems to indicate that the rate-determining step in the overall reaction is the isomerization of the adduct (VI_a) to the diazo nitrate (VII_a). However, if this is true then no contribution to the high positive entropy of activation from the decomposition of the diazonium nitrate is possible. Therefore, another plausible explanation of the data is that after the complex (VI_a) is formed it acquires energy, becomes activated, and rearranges to the diazo nitrate (VII_a) accompanied by an increase in entropy. The diazo nitrate (VII_a) might then become activated and decompose with another increase in entropy to yield the intermediates which are necessary to form the observed products (II_a, III_a, IV_a). Since no known bands[9] characteristic of diazonium salts appear in the infrared spectrum of the reaction mixture, it would seem likely that the energy of activation of this process is lower than that necessary to activate the complex (VI_a) and only very small quantities would be present at any given time. The contribution of this process to the activation entropy of the overall reaction would probably be smaller than that of the isomerization of the complex (VI_a) to the diazo nitrate (VII_a).[10]

EXPERIMENTAL

Materials. Bisnitrosocyclohexane was prepared by the oxidation of *N*-cyclohexylhydroxylamine.[11] Cyclohexyl nitrate and cyclohexyl nitrite were prepared by the esterification of cyclohexanol.[12] Nitrocyclohexane was purified by repeated distillation under reduced pressure. The cyclohexane used as a solvent was distilled through an 18 in. Vigreux column.

Apparatus. The apparatus employed was a Parr low pressure shaker bomb. An electrically heated insulated bottle with a thermocouple attached to read the inside temperature was used to contain the reaction mixture. In this equipment, it was possible to maintain the temperature within three-tenths degree of the desired reading.

Analytical method. Because the concentration of reaction products was less than 0.2% a 1.0 mm. infrared cell was employed. The following instrumental conditions were used on the Perkin Elmer Model 21 spectrophotometer.

Resolution, 9.84	Speed, 3
Response, 1	Suppression, 0
Gain, 6	

The absorption bands used to measure the concentration of each major product as well as the concentration range covered in preparing the working curves are given below.

Component	Band	Base Point	Concn. Range
Nitrosocyclohexane	8.28	8.60	0–0.2 g./100 ml.
Nitrocyclohexane	6.44	5.50	0–0.2 g./100 ml.
Cyclohexyl nitrate	6.10	5.50	0–0.06 g./100 ml.

Distilled cyclohexane was used as solvent and as blank in each case. The working curves of concentration versus absorbance gave excellent agreement with Beer's Law.

Synthetic samples were prepared and analyzed with the following results.

	Concn. in G./100 Ml.		
	Bisnitrosocyclohexane	Nitrocyclohexane	Cyclohexyl Nitrate
Present	0.136	0.0025	0.0017
Found	0.135	0.0030	0.0017
Present	0.107	0.0617	0.0168
Found	0.107	0.0625	0.0168
Present	0.0450	0.0247	0.0420
Found	0.0455	0.0260	0.0423

In order to analyze actual samples taken in the rate study, oxides of nitrogen had to be removed from the solution. This was accomplished by washing 100 ml. of the cyclohexane solution twice with 50 ml. of distilled water. The major products were not affected significantly.

Bisnitrosocyclohexane (G./100 Ml.)	
Before Wash	After Wash
0.0500	0.0490
0.0515	0.0515
0.0420	0.0415

In reactions of nitric oxide with the nitroso dimer at 25°, 90–100% of the products were accounted for as cyclohexyl nitrate and nitrocyclohexane during the first hour of reaction. After 2 hr. of reaction 70–80% of the products consisted of the same two compounds. At this point, cyclohexyl nitrite and carbonyl compounds which probably were formed as a result of the build up of nitrogen dioxide in the system[2,13] began to appear as products. After 17 hr., 65–70% of the products were still accounted for as nitrocyclohexane and cyclohexyl nitrate. Nitrogen dioxide is known to oxidize cyclohexyl nitrite to mixtures of dibasic acids.[13] This might account for the presence of the carbonyl compounds. The infrared absorption of the nitrite ester can be seen as a shoulder on the nitrate band in Figure 3. Other products present were polynitrocyclohexanes which absorb at lower wavelengths in the infrared than nitrocyclohexane (6.35–6.40 μ) and appear in Figures 2 and 3 as a shoulder on the nitro band in Figures 2 and 3.

Cyclohexyl nitrate was always the major product. The ratio of the nitrate to nitrocyclohexane varied with the reaction time and temperature. The ratio of nitrate to nitroparaffin for 70% consumption of the nitroso dimer was always near 3:1 regardless of time or temperature.

Although all solutions were analyzed within 15 min. after being taken from the constant temperature bath and washed, a check was made on their stability at room temperature. The following results indicated that the washed solutions were relatively stable.

Time (hr.)	0.25	4.0	6.0	24
	Concn. in G./100 Ml.			
Bisnitrosocyclohexane	0.081	0.078	0.076	0.072
Nitrocyclohexane	0.005	0.007	0.008	0.015
Cyclohexyl nitrate	0.010	0.010	0.010	0.010

Procedure. The samples were prepared by dissolving approximately 0.5 g. of bisnitrosocyclohexane in distilled cyclohexane and diluting the solution to 1 l. One hundred milliliters of this solution was placed in the pressure bottle. The bottle was sealed and brought to the desired temperature. Nitric oxide was then admitted to the bottle at the pressure desired. Agitation was started and the sample al-

(10) De Tar and Kwong, *J. Am. Chem. Soc.*, 78, 3921 (1956).

(11) Muller and Metzger, *Chem. Ber.*, 88, 165 (1955).

(12) Kornblum and Teitelbaum, *J. Am. Chem. Soc.*, 74, 3076 (1952).

(13) Doumani, Coe, and Attane (To Union Oil Co.), U. S. Patent 2,465,984 (1949).

lowed to shake for the required time period. The sample was then removed, washed with two 50 ml. portions of distilled water, passed through a filter paper to remove traces of water, and analyzed for bisnitrosocyclohexane, nitrocyclohexane, and cyclohexyl nitrate. These operations were repeated at various intervals of time under identical conditions of temperature and pressure until sufficient data were obtained to make the necessary calculations for the desired pressure and temperature. All reactions were carried to at least 70% consumption of the nitroso dimer.

Handling of data. The rate constants were calculated by integration of the first order rate expression using two widely separated time limits[14] and from the slope of the plot of the logarithm of the concentration of bisnitrosocyclohexane *vs.* time. The slope was determined statistically by the method of least mean squares.[15,16] The agreement between the two methods was excellent. The rate constant at 51° was determined by measuring the half-life of bisnitrosocyclohexane under the usual reaction conditions and calculating the rate constant from the half-life.[14]

The activation energy (E_a) was determined from the slope of the curve obtained by plotting the logarithm of the rate constant at various temperatures *vs.* the reciprocal of the absolute temperature[14] and determining the slope of the curve by the method of least mean squares.[15,16] $\Delta H\ddagger$ was determined from the relationship.[6]

$$\Delta H\ddagger = E_A - RT$$

The entropies of activation were calculated from the Eyring equation.[6]

Acknowledgments. The services of Mr. J. L. Swyler and Mr. G. Gesty who carried out the experimental work are deeply appreciated.

The advice and consultation of Dr. G. R. Coraor, Dr. J. D. Roberts, and Dr. C. Gardner Swain were invaluable in carrying out this investigation.

WILMINGTON, DEL.

(14) Getman and Daniels, *Outlines of Physical Chemistry*, p. 342–386, John Wiley and Sons, Inc., New York, 1947.

(15) Roseveare, *J. Am. Chem. Soc.*, **53**, 1651 (1931).

(16) Reed and Theriault, *J. Phys. Chem.*, **35**, 673 (1931)

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ETHYL CORPORATION]

ortho-Alkylation of Aromatic Amines[1]

GEORGE G. ECKE, JOHN P. NAPOLITANO, ALLEN H. FILBEY, AND ALFRED J. KOLKA[2]

Received November 5, 1956

Primary and secondary aromatic amines react with olefins in the presence of aluminum anilide type catalysts to yield products alkylated in the *ortho* positions. No *para* alkylated products were detected.

The nuclear alkylation of aromatic amines by aluminum halide catalyzed reactions has not found wide application because of complications arising from the characteristics of the amino group. It was recently found in these laboratories that primary and secondary aromatic amines could be alkylated with olefins using the corresponding aluminum anilide as the catalyst to give products from which only *ortho*-alkylated amines could be isolated.

An investigation of the process has made several generalizations possible in regard to the reactivities of the reactants (Table I) and the structures of

TABLE I

REACTIONS OF AROMATIC AMINES WITH OLEFINS USING N-ALUMINO CATALYSTS

Reactants		Temperature, °C	Operating Pressure Range, psi	Reaction Time, Hours	Recovered Amine, Mole %	2-Alkyl-Amine Mole %	2,6-Di-Alkylamine Mole %
Olefin	Amine						
Ethylene	Aniline	330	450–500	24	29	33	20
Ethylene[a]	Aniline[a]	330	600–800	9	1	2	90[b]
Ethylene	*N*-Methylaniline	205	600–800	3	—	86	—
Ethylene	*N*-Ethylaniline	205	600–800	2.5	2	86	—
Ethylene	*o*-Toluidine	325	600–800	8	—	—	90
Ethylene	α-Naphthylamine	300	600–800	3	55	30	—
Ethylene	*N*-Ethyl-*m*-chloroaniline	255	600–800	3	3	85[c]	—
Propylene	Aniline	330	600–800	5	81	4	—
Propylene	*N*-Methylaniline	235	500–700	4	32	54	—
Isobutylene	Aniline	330	720–730	3	92	2	—
Decene	*N*-Methylaniline	300	90–100	0.5	—	35	—
Cyclohexene	*N*-Methylaniline	300	280–300 (vapor pressure)	0.5	89	2	—

[a] This reaction was carried out using 6.7 mole % of aluminum anilide as compared with 3–4 mole % of catalyst in the other experiments. [b] The dialkylated product consisted of 86% of 2,6-diethylaniline and 4% of 2-ethyl-6-*sec*-butylaniline. [c] Approximately equal amounts of *N*-ethyl-2-ethyl-3-chloroaniline and *N*-ethyl-2-ethyl-5-chloroaniline were produced.

(1) Presented in part before the Division of Organic Chemistry at the 130th meeting of the AMERICAN CHEMICAL SOCIETY, Atlantic City, N. J., Sept., 1956 and in a preliminary communication, *J. Org. Chem.*, 21, 711 (1956).

(2) Present address, Koppers Co., Inc., Koppers Bldg., Pittsburgh, Pa.

the products (Table II): (1) That only *ortho* alkylated products arise from the reaction; (2) That the reactivities of different types of olefins are $CH_2{=}CH_2 > CH_2{=}CHR > RCH{=}CHR$ or $CH_2{=}CR_2$; (3) That the olefin becomes attached to the aromatic ring at the olefinic carbon atom possessing the larger number of alkyl groups; (4) That *N*-alkylanilines are more reactive than the corresponding primary anilines, although only one alkyl group can be introduced into the ring.

TABLE II

PROPERTIES AND ANALYSES OF ALKYLATION PRODUCTS

Compound	B.P., °C	n_D^{20}	Nitrogen, % Calcd.	Found
2-Ethylaniline[a]	209–210	1.5602	11.6	11.4
2,6-Diethylaniline	235–236	1.5461	9.4	9.8
2-Ethyl-6-*sec*-butylaniline	152–153 at 30 mm.	1.5339	7.9	7.9
N-Methyl-2-ethylaniline	216.5	1.5553	10.4	10.9
N-Ethyl-2-ethylaniline	223	1.5398	9.4	9.6
2-Methyl-6-ethylaniline	224	1.5525	10.4	10.6
2-Ethyl-1-naphthylamine[b]	189–190 at 20 mm.	1.6474[c]	8.2	8.2
N-Ethyl-2-ethyl-3-chloroaniline	150.5–151.5 at 30 mm.	1.5556	7.6	8.1[d]
N-Ethyl-2-ethyl-5-chloroaniline	157.5–158.2 at 30 mm.	1.5544		
2-Isopropylaniline[e]	217–218	1.5483	10.3	10.4
2-*tert*-Butylaniline[f]	227–228	1.5450	9.5	9.7
N-Methyl-2-isopropylaniline	224	1.5460	9.4	9.6
N-Methyl-2-(1-Methylnonyl) aniline	138 at 2 mm.	1.5134	5.7	6.0
N-Methyl-2-cyclohexylaniline	112–117 at 2 mm.	1.5644	7.4	7.6

[a] Acetyl derivative m.p. 111–112°, thiourea m.p. 120–120.5°. Braun, Bayer, and Blessing, *Ber.*, **57B**, 392 (1924) report corresponding derivatives of 2-ethylaniline to melt at 113° and 124°. [b] Acetyl derivative m.p. 155–156.5°, Levy, *Ann. chim.*, **9**, 58, (1938) reports the acetyl derivative of 2-ethyl-1-naphthylamine to melt at 156.5°. [c] n_D^{25}. [d] Analysis of mixture of two isomers before refractionation. [e] Phenylthiourea m.p. 134.5–135.5°, hydrochloride m.p. 182–185°, picrate m.p. 159–161° (dec.). Brown, Bayer and Blessing, *Ber.* **57**, 397 (1924) report corresponding derivatives of 2-isopropylaniline to melt at 129–130°, 182°, and 160°. [f] Acetyl derivative m.p. 161.5–162.5°. Craig, *J. Am. Chem. Soc.*, **57**, 195 (1935) reports the acetyl derivative of 2-*tert*-butyl-aniline to melt at 159–161°.

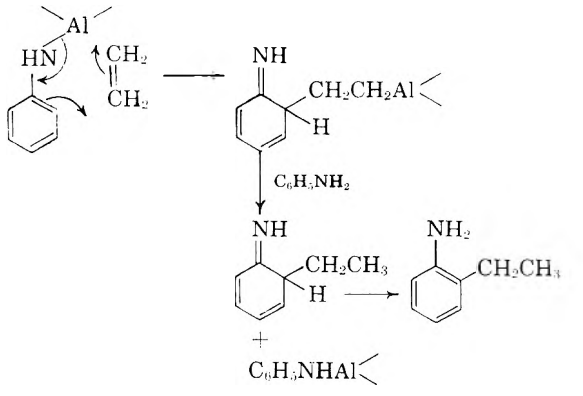
TABLE III

DERIVATIVES OF NEW COMPOUNDS PRODUCED BY ALKYLATION REACTION

Amine	Derivative	M.P., °C	Analysis (% N) Calcd.	Found
2,6-Diethylaniline	Acetyl	135–136	7.34	7.26
2-Ethyl-6-*sec*-butylaniline	Benzoyl	198.5–199.5	4.98	4.68
N-Methyl-2-ethylaniline	NO_2BS[a]	133.5–134	8.75	9.07
N-Ethyl-2-ethylaniline	NO_2BS	117.5–118	8.38	8.22
	Benzoyl	47–48	5.53	5.76
2-Methyl-6-ethylaniline	Acetyl	126.5–127.5	8.75	9.07
N-Ethyl-2-ethyl-3-chloro-aniline	Hydrochloride	114–115	6.37	6.21
N-Ethyl-2-ethyl-5-chloro-aniline	Hydrochloride	115–116	6.37	6.19
N-Methyl-2-isopropylaniline	NO_2BS	103–104.5	8.38	8.43

[a] *meta*-Nitrobenzenesulfonyl derivative.

While these observations are inadequate to permit any conclusion to be reached in regard to the mechanism of the reaction, they do provide a basis for the formulation of a hypothesis regarding the nature of the process. Thus, the complete predominance of the *ortho*-alkylated products strongly suggests the geometry imposed by a cyclic intermediate. Since the reactivities of the different types of olefins is that observed in carbanion reactions[3] and is the inverse of that observed in carbonium ion reactions, it would appear that the process, although concerted, is fundamentally a carbanion or free radical type of reaction. An ionic electron shift has been indicated in the equations, although there is no basis for excluding the free radical mechanism at this point. The direction of electron shift, if an ionic process, is indicated by the fact that the olefin becomes attached at the more highly substituted carbon atom.



It might be expected that in both the carbanion

(3) Pines and Mark, *J. Am. Chem. Soc.*, **78**, 4319 (1956).

and free radical mechanisms the reactivity of the amine would be increased by the presence of an *N*-alkyl group. The failure of the *N*-alkyl amines to react at the second *ortho*-position may result from steric hindrance between the *N*-alkyl and the *ortho*-alkyl group preventing the nitrogen atom from rotating to the angle requisite for the formation of the cyclic intermediate.

Several other mechanisms can be written based on analogy with the aluminum halide catalyzed alkylation of aromatic compounds. These alternatives would be fundamentally carbonium ion type reactions in which the initiation would arise from the interaction of the anilide and the amine:

$$C_6H_5NHR + (C_6H_5NR)_3Al \longrightarrow (C_6H_5NR)_4Al^- + H^+$$

Such a mechanism should exhibit the relative reactivities of different types of olefins typical of acid-catalyzed reactions, which are the inverse of those observed in the *ortho*-alkylation of amines.

The fact that *N*-ethyl-3-chloroaniline required a higher temperature for ethylation than did *N*-ethylaniline suggests partial deactivation of the ring by the electron-withdrawing chlorine atom. It was also of interest that approximately equal amounts of the 2- and the 6-ethyl isomers were produced. This would suggest that the chlorine atom did not cause appreciable steric hindrance.

The presence of 2-ethyl-6-*sec*-butylaniline in the product from the ethylation of aniline was unexpected; however mass spectrometer analysis of a sample of the gas from the autoclave at the conclusion of the ethylation revealed the presence of a small amount of butene (0.8%). Presumably a higher concentration may have been present in the liquid phase, and some alkylation with the butene may have occurred.

EXPERIMENTAL[4]

Preparation of catalysts. The aluminum anilides used as catalysts were prepared by the same general method described in the patent literature.[5] A mixture of 300 ml. of the amine and 4.5 g. (one-sixth formula wt.) of aluminum turnings[6] were stirred and heated under a nitrogen atmosphere until hydrogen evolution became apparent. In the case of aniline, reaction was apparent at 150°. The mixture was stirred and heated until the aluminum had reacted completely. After cooling, the solution was transferred to the autoclave along with an additional 200–300 ml. of the amine. Care was taken throughout the preparation to protect the mixture from moisture and oxygen.

An alternate procedure involved heating the aromatic amine and the aluminum chips in the sealed autoclave until a pressure rise, caused by the evolved hydrogen, became evident. The mixture was then cooled and the hydrogen vented. Somewhat higher temperatures were required to effect catalyst formation by this method, but the resultant catalysts had the same activity as those prepared in glass equipment.

Alkylation procedure. The alkylations were carried out in a two-liter steel autoclave equipped with an anchor-type stirrer (57 r.p.m.) thermocouple well, charging lines, and blow-out disc. After charging the catalyst as described above, the autoclave was flushed with nitrogen and sealed. The stirrer was then started and the mixture heated to 100–150° at which point sufficient olefin was added to give 200–500 p.s.i. of pressure. Heating was then resumed until a temperature was reached where reaction was apparent from a drop in pressure. This temperature was maintained and the autoclave repressured with olefin as required.[7] The reactions were usually continued until the rate of olefin pressure drop became negligible, although in some cases the reaction was stopped before completion. Data on reaction conditions are presented in Table I.

After cooling to room temperature, the pressure was vented and the catalyst hydrolyzed by the addition of water. The aluminum hydroxide was removed by filtration and the water layer separated. The organic layer was again washed and dried by azeotropic distillation with toluene. Fractionation of the product was effected through an appropriate helix-packed column (30–60 theoretical plates). The boiling points, refractive indices and analyses of the products are reported in Table II.

Proof of structure of 2,6-diethylaniline. A 41.1 g. (0.276 mole) portion of the aniline ethylation product boiling at 235–236° was added to a solution of 85 ml. of sulfuric acid in 120 ml. of water. Ice (200 g.) was then added and the mixture maintained at 0–5° by the addition of more ice while 28 g. (0.406 mole) of sodium nitrite dissolved in 60 ml. of water was added. After permitting the mixture to warm to room temperature and remain there for 24 hr., the organic layer was removed. The product was dissolved in 10% sodium hydroxide solution to effect separation from non-phenolic materials and the phenolic compound then liberated by acidification. The product was separated and distilled from a Claisen flask to yield 23.5 g. (57% theory) of 2,6-diethylphenol (b.p. 110–111° at 16 mm.; m.p. 37–37.5°). The melting point of the product was not depressed when mixed with an authentic sample of 2,6-diethylphenol.

Proof of structure of 2-ethyl-6-sec-butylaniline. A 17.7 g. (0.1 mole) quantity of the aniline ethylation product boiling 152–153° (30 mm.) was converted to the corresponding phenol using the diazotization procedure of the above experiment. There was obtained 10 g. (56% theory) of 2-ethyl-6-*sec*-butylphenol (b.p. 85–88° at 2 mm.; n_D^{20} 1.5167), which was identified by comparison with the product of a reaction of 2-ethylphenol and 1-butene.[8] The two samples of the 2-ethyl-6-*sec*-butylphenol had identical infrared spectra and a mixed melting point of the phenylurethanes (m.p. 131.5–133°) showed no depression.

Proof of structure of 2-methyl-6-ethylaniline. A 51.3 g. (0.378 mole) portion of 2-methyl-6-ethylaniline was converted to 2-methyl-6-ethylphenol by the procedure used on the corresponding 2,6-diethyl compound. There was obtained 28 g. (55% theory) of 2-methyl-6-ethylphenol. (b.p. 101–103° at 17 mm.). The phenylurethan of the product was found to melt at 150–151°. (lit. m.p. 150–151°).[9]

Proof of structure of N-ethyl-2-ethylaniline. A mixture of 106 g. (0.87 mole) of 2-ethylaniline and 99 g. (1.0 mole) of potassium carbonate was refluxed with 156 g. (1.0 mole) of ethyl iodide for 1 hr. After washing with 10% potassium

(4) All melting points and boiling points are uncorrected.

(5) D. R. P. 287601. *Chem. Zentr.*, 1915, II, 992.

(6) The aluminum chips were machined from aluminum metal containing less than one percent of impurities as estimated by spectrographic analysis. The use of aluminum of lower purity was found to necessitate the use of somewhat higher temperatures for catalyst formation.

(7) Ethylene was charged directly from the supply cylinder. Propylene and isobutylene were charged from a specially constructed heated supply tank. Cyclohexene and decene were charged directly to the autoclave along with the amine and the catalyst before heating.

(8) Kolka, Napolitano, Filbey, and Ecke, *J. Org. Chem.*, 22, 642 (1957).

(9) von Auwers, Bundesmann, and Weiners, *Ann.*, 447, 180 (1926).

hydroxide and with water, the organic layer was separated and fractionated. There was obtained 58 g. (44% theory) of *N*-ethyl-2-ethylaniline (b.p. 117–117.5° at 20 mm., n_D^{20} 1.5398). The benzoyl derivative (m.p. 46.5–48°) and the 3-nitrobenzenesulfonyl derivative (m.p. 116–117°) of this compound were prepared. The mixed melting points of these derivatives with the corresponding ones of the ethylation product of *N*-ethyl-aniline were not depressed.

Synthesis of N-ethyl-2-ethyl-5-chloroaniline. The following synthesis of *N*-ethyl-2-ethyl-5-chloroaniline was carried out to elucidate the structure of the products from the ethylation of *N*-ethyl-3-chloroaniline.

Nitration of 1-chloro-4-ethylbenzene. Fractionation of practical grade 1-chloro-4-ethylbenzene (Distillation Products Industries) through a 60-plate column yielded the pure isomer (b.p. 182°; n_D^{20} 1.5174).[10] Nitration of this material was effected in two batches. In the first reaction 281 g. (2.0 moles) of 1-chloro-4-ethylbenzene was dispersed in 500 g. of 80% (wt.) sulfuric acid and maintained at 35–40° while a solution of 187 g. of concentrated nitric acid in 460 g. of concentrated sulfuric acid was added over a 35-min. period. The mixture was then heated to 90° and maintained at that temperature for 30 min. After cooling, the product was poured over ice and the organic layer separated. A second nitration was carried out using 369 g. (2.63 moles) of 1-chloro-4-ethylbenzene and proportional amounts of acid, and the product combined with that of the first nitration. After washing with water and with 10% sodium carbonate solution, the product was dried and distilled through a 20-plate column to yield 624 g. (73% theory) of mononitrated product (b.p. 144–160° at 29 mm.). Refractionation through a 60-plate column resulted in the separation of two isomers. There was obtained 286 g. of a low boiling isomer, I, (b.p. 147° at 30 mm.; n_D^{20} 1.5518) and 292 g. of a high boiling isomer, II, (b.p. 162° at 30 mm.; n_D^{20} 1.5499).

Oxidation of I in basic solution with potassium permanganate showed it to be 2-nitro-4-chloroethylbenzene in that the product was 2-nitro-4-chlorobenzoic acid, m.p. 141–142° (lit. m.p. 140–141°).[11] Similarly II was shown to be 3-nitro-4-chloroethylbenzene by oxidation to 3-nitro-4-chlorobenzoic acid, m.p. 180–181.5°, (lit. m.p. 180°).[12]

Reduction of 2-nitro-4-chloroethylbenzene. A total of 216 g. (1.16 moles) of I was reduced in two batches with stannous chloride following the procedure employed by Gray and Bonner for the reduction of 4-methoxy-3-nitroacetophenone.[13] After freeing the amine by treating the reaction product with sodium hydroxide, the product was separated, dried, and fractionated to yield 150 g. (83%) of 2-ethyl-5-chloroaniline (b.p. 155° at 33 mm.; n_D^{20} 1.5742).

Acetylation of 2-ethyl-5-chloroaniline. A 128 g. (0.83 mole) portion of 2-ethyl-5-chloroaniline was treated with 93 g. (0.91 mole) of acetic anhydride and the product recrystallized from ethanol to yield 115 g. (70% theory) of 2-ethyl-5-chloroacetanilide (m.p. 140–141°).

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12. Found: C, 61.2; H, 5.97.

Reduction of 2-ethyl-5-chloroacetanilide. A solution of 11.4 g. (0.3 mole) of lithium aluminum hydride in 1200 ml. of ether was heated to boiling and the reflux from a Soxhlet extractor used for the addition of 79 g. (0.4 mole) of 2-ethyl-5-chloroacetanilide. The product was hydrolyzed by the addition of water and the product separated by ether and benzene extractions. Fractionation of the combined extracts yielded 41 g. (56% theory) of *N*-ethyl-2-ethyl-5-chloroaniline (b.p. 127° at 26 mm.; n_D^{20} 1.5552). There was also obtained 12 g. of unreduced 2-ethyl-5-chloroacetanilide. The infrared spectrum of this material was identical with that of the higher boiling isomer from the ethylation of *N*-ethyl-3-chloroaniline. Further proof of the identity was obtained by the preparation of the hydrochloride of the synthesis product (m.p. 115–116°) and determining mixed melting points with the hydrochlorides of the two isomeric ethylation products, (Table III). The mixed melting point with the hydrochloride of the high boiling isomer was undepressed (115–116°) while that of the hydrochloride of the low boiling isomer was depressed (93–110°). It is thus apparent that the high boiling isomer is *N*-ethyl-2-ethyl-5-chloroaniline, and by inference the low boiling isomer must be *N*-ethyl-2-ethyl-3-chloroaniline.

Acknowledgment. The authors wish to express their appreciation to Dr. Rex D. Closson for helpful suggestions in the undertaking of this investigation.

DETROIT 20, MICH.

(10) Martin, *Ind. Eng. Chem.*, 41, 2876 (1949) has reported 1-chloro-4-ethylbenzene to boil at 184.42° (Corr.) and to have a refractive index n_D^{20} 1.5175.

(11) Green and Lawson, *J. Chem. Soc.*, 59, 1019 (1891).

(12) King and Murch, *J. Chem. Soc.*, 127, 2646 (1925).

(13) Gray and Bonner, *J. Am. Chem. Soc.*, 70, 1251 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ETHYL CORPORATION]

The *ortho*-Alkylation of Phenols[1]

ALFRED J. KOLKA,[2] JOHN P. NAPOLITANO, ALLEN H. FILBEY, AND GEORGE G. ECKE

Received November 5, 1956

The reaction of phenols with olefins in the presence of aluminum phenoxide-type catalysts has been investigated and under proper reaction conditions found capable of yielding predominantly 2-alkyl and 2,6-dialkylphenols. The mechanism of the reaction is discussed.

The alkylation of phenols has been conducted with a variety of catalysts and alkylating agents.[3] In the majority of cases *para*-alkylation was the predominant mode of reaction. The preparation of 2,6-dialkylphenols by direct alkylation was found to be difficult. Unless the *para* position was blocked, very little, and in some instances, no 2,6-dialkylphenols were obtained. To prepare 2,6-dialkylphenols multistep syntheses have been used. Thus 2,6-di-*tert*-butylphenol had been prepared only by the

(1) Presented in part before the Division of Organic Chemistry at the 130th meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1956 and in a preliminary Communication, *J. Org. Chem.*, 21, 712 (1956).

(2) Present address, Koppers Co., Inc., Koppers Bldg., Pittsburgh, Pa.

(3) Price, *Org. Reactions*, III, 58 (1946).

TABLE I

COMPOSITION OF PHENOL-ISOBUTYLENE ALKYLATION PRODUCTS (MOLE PERCENT)

Experiment No.	1	2	3	4	5
Reaction temperature (°C.)	65–68	105–115	115–168	300–320	150–190
Length of run (hr.)	3	3.5	1.3	0.8	4
Isobutylene pressure (p.s.i.)	0–95	30–100	50–200	180–360	Atm.
Phenol	27	5	7	46	71
Phenyl *tert*-butyl ether	12	—	—	—	—
2-*tert*-Butylphenol	43	46	52	7	—
4-*tert*-Butylphenol	1	1	2	33	14
2,6-Di-*tert*-butylphenol	5	36	12	—	—
2,4-Di-*tert*-butylphenol	2	5	15	3	—
2,4,6-Tri-*tert*-butylphenol	—	6	6	2	—

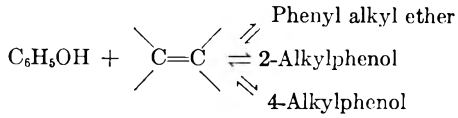
alkylation of the para-halophenol followed by removal of the para-halogen.[4] This paper describes the use of a new type of catalyst, the aluminum phenoxides, with which phenolic compounds may be directly alkylated with olefins to yield products containing a high percentage of 2-alkyl- and 2,6-dialkylphenols. Minor amounts of the ethers of phenol and of 2-alkylphenol were obtained in the products of those runs carried out at minimum reaction temperatures.

When phenol was alkylated with ethylene or propylene in the presence of aluminum phenoxide, no 4-alkylphenol was detected in any product under the reaction conditions used in the investigation. However, when isobutylene was used as the alkylating agent, the variation of product composition with changes in reaction variables became much more significant. Here again it was found that some ether production resulted from low temperature operation (Table I, Exp. 1). A much more serious complication was the appearance of *para*-substituted phenols in the products of the runs at higher temperatures. The extreme case was that of a reaction carried out at atmospheric pressure and relatively high temperatures (Table I, Exp. 5) in which 4-*tert*-butylphenol was the only alkylation product.

Under suitable reaction conditions, aluminum phenoxide catalyst was found to be highly selective even when isobutylene was used as the olefinic reactant; the alkylation of phenol with this olefin gave a 74% yield of 2,6-di-*tert*-butylphenol. Since the olefin feed system used differed from those used in the other experiments, this result is not included in Table I, but may be found under Experimental.

A group of simple dealkylation experiments was carried out to determine the cause of the variation in product composition. It was found that phenyl *tert*-butyl ether as well as both the 2- and the 4-*tert*-butylphenols were stable at their normal boiling points in the absence of catalyst. However, in the presence of aluminum phenoxide the ether is readily dealkylated at 100°, 2-*tert*-butylphenol is rapidly dealkylated at 190°, but 4-*tert*-butylphenol is stable even at its boiling point (236°). From these experiments, the factors controlling product composition are apparent.

The specificity of the reaction is the result of the rates and equilibria of a group of competing reactions.



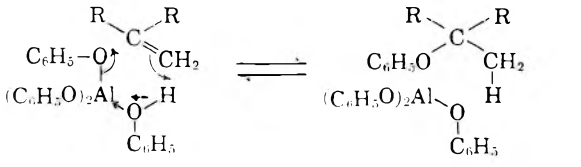
To account for the formation of predominantly ether and *ortho*-alkylphenols, the rate of formation of these compounds must be much faster than the rate of formation of the *para*-isomer. However, these compounds are not thermodynamically the most stable products, at least at elevated temperatures, and it is necessary that the reaction be stopped before equilibrium is attained or else *para*-substituted products may be expected to predominate. Thus it is obvious that the experiment carried out at atmospheric pressure and high temperatures would promote the reverse reactions of the unstable products by simple mass action principle. Conversely, a reaction carried out at relatively low temperature, with high olefin concentration, and with an optimum reaction time should achieve maximum *ortho*-isomer concentration; these were the conditions used to effect a 74% conversion to 2,6-di-*tert*-butylphenol.

It is of interest to give some consideration to the mechanism of the aluminum phenoxide catalyzed reaction. The reactivity of different types of olefins in the reaction is typical of carbonium ion type reactions ($R_2C{=}CH_2 > RCH{=}CH_2$ or $RCH{=}CHR > CH_2{=}CH_2$). The elegant investigation of the aluminum alkoxides by Meerwein and Bersin[5] has shown that such compounds tend to coordinate with a molecule of alcohol to form acid solutions which may be titrated with alcoholic sodium alkoxide to the thymophthalein end point and the formation of a salt, $NaAl(OR)_4$. Although the acid, $HAl(OR)_4$ could not be isolated except as its metal salts, there is no reason to doubt its existence. Such behavior is analogous to that of the aluminim hal-

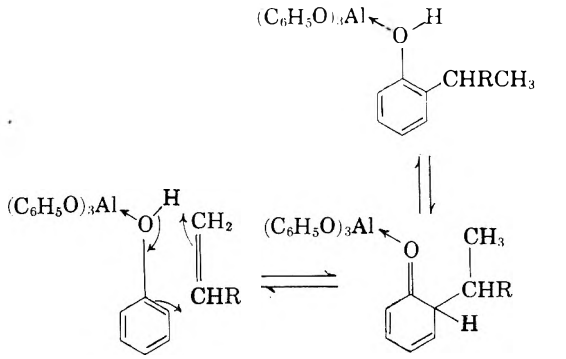
(4) Stillson and Sawyer, U. S. Patent 2,459,597 (January 18, 1949); Hart and Cassis, *J. Am. Chem. Soc.*, **73**, 3179 (1951).

(5) Meerwein and Bersin, *Ann.*, **476**, 113 (1929).

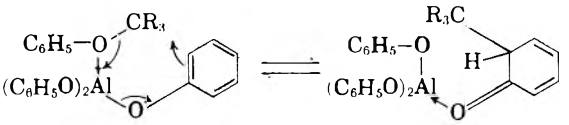
ides. The role of halogen acids and aluminum halides in forming σ complexes with aromatic hydrocarbons[6] and of alkyl halide-aluminum halide complexes in Friedel-Crafts alkylations of aromatic hydrocarbons[7] illustrates the tendency of aluminum halides to participate in AlX_4^- complexes. It might then reasonably be assumed that as a derivative of an acid of intermediate strength, aluminum phenoxide would exhibit properties intermediate to those of the aluminum alkoxides and the aluminum halides. As such it might be expected to complex with a molecule of phenol to give an acid, $HAl(OC_6H_5)_4$.



Ether formation.



Direct *ortho*-alkylation



Ortho-Alkylation *via* ether

Such a complex possesses a geometry ideally suited for reaction with olefins in several six-membered ring concerted mechanisms. There is also the interesting question as to whether the aromatic rings in such a complex are activated or deactivated. In any case it must be kept in mind that the thermodynamics of the reaction are not altered, and the success of aluminum phenoxide as an *ortho*-alkylation catalyst must be attributed both to its selectivity for *ortho*-alkylation and its moderate catalytic activity, which permits the accumulation of the unstable *ortho*-alkylation products.

(6) Brown and Pearsall, *J. Am. Chem. Soc.*, **74**, 191 (1952).

(7) Brown and Grayson, *J. Am. Chem. Soc.*, **75**, 6285 (1953); Brown and Wallace, *J. Am. Chem. Soc.*, **75**, 6279 (1953).

EXPERIMENTAL[8]

Alkylation of phenol with ethylene. The aluminum phenoxide catalyst was prepared by adding 4.5 g. ($^1/_6$ formula wt.) of aluminum turnings in small amounts and with vigorous stirring to 300 g. of phenol at 165° under a nitrogen atmosphere. When hydrogen evolution had ceased, the mixture was cooled and transferred along with an additional 300 g. of phenol to a 2-l. steel autoclave. The catalyst preparation and the transfer process were carried out under a nitrogen atmosphere to protect the material from oxygen and moisture. The stirrer was started and the autoclave heated to 200° at which point ethylene was added to give 500 p.s.i. total pressure. Heating was resumed, and when the temperature reached 280° a drop in pressure was noted. More ethylene was then added to raise the pressure to 800 p.s.i. and the pressure maintained at 600 to 800 p.s.i. by repressuring when necessary. The temperature was maintained between 280° and 320° and a 2100-p.s.i. pressure drop noted over a 10-hr. period. After cooling, the product was removed from the autoclave and shaken with 200 ml. of 5% hydrochloric acid. The mixture was filtered prior to removing the aqueous phase. After washing twice with water, toluene was added and the product dried by azeotropic distillation. The product was fractionally distilled to yield 259 g. (43%) of recovered phenol, 189 g. (24%) of 2-ethylphenol, 79 g. (8%) of 2,6-diethylphenol and 63 g. of higher boiling material.

About 8 g. (1%) of phenyl ethyl ether was also obtained as a caustic insoluble material from the fraction boiling below phenol. Identification was based upon its physical properties (m.p. −31 to −30°, b.p. 165–167°, n_D^{20} 1.5066). The 2-ethylphenol boiled at 201–202° and had a refractive index (n_D^{20}) of 1.5372.

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.3; H, 8.11.

The aryloxyacetic acid derivative of the 2-ethylphenol was prepared and found to melt at 138–140° (lit. m.p. 140–141°).[9]

The 2,6-diethylphenol boiled at 219° and after recrystallization from hexanes melted at 37–38° (lit. m.p. 37.5–38°).[10]

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.4; H, 9.22.

The phenyl urethan of 2,6-diethylphenol was prepared and upon recrystallization from benzene found to melt at 170-171°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: N, 5.20. Found: N, 5.31.

The aryloxyacetic acid derivative of 2,6-diethylphenol, recrystallized from isooctane, melted at 67–68°.

Anal. Calcd. for $C_{12}H_{16}O_3$: Neut. Equiv., 208. Found: neut. equiv., 204.

Alkylation of phenol with propylene. The autoclave was charged with a phenol–aluminum phenoxide mixture prepared from 565 g. (6 moles) of phenol and 4.5 g. ($^1/_6$ formula wt.) of aluminum turnings as in the above experiment. Propylene was charged to the autoclave as required from a specially constructed heated propylene supply cylinder. Alkylation was effected at 240° over a 2-hr. period using incremental propylene addition at 200 to 500 p.s.i. The product was processed as in the above ethylation to yield 656 g. (61%) of 2,6-diisopropylphenol (m.p. 19°, b.p. 136° at 30 mm., n_D^{20} 1.5139, d_4^{20} 0.955).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.8; H, 10.2.

Proof of structure of 2,6-diisopropylphenol. A solution of 35 g. (0.2 mole) of 2,6-diisopropylphenol, 34 g. (0.25 mole) of sulfuryl chloride, and one drop of pyridine was warmed slightly whereupon a vigorous evolution of gas resulted.

(8) All melting points and boiling points are uncorrected.

(9) Steinkopf and Hopner, *J. prakt. Chem.* [2], **113**, 140 (1926).

(10) von Auwers and Wittig, *Ber.*, **57**, 1275 (1924).

The mixture was heated to 100° to insure complete reaction. Fractionation of the product yielded 24 g. (56%) of 2,6-diisopropyl-4-chlorophenol (b.p. 152–153° at 17 mm., n_D^{20} 1.5291).

Anal. Calcd. for $C_{12}H_{17}OCl$: Cl, 16.7. Found: Cl, 16.9.

The infrared spectrum of this material was identical with that of the 2,6-diisopropyl-4-chlorophenol obtained in the following experiment.

Alkylation of 4-chlorophenol with propylene. The catalyst was prepared by heating 386 g. (3 moles) of 4-chlorophenol and 100 ml. of toluene with 2.25 g. ($^1/_{12}$ formula wt.) of aluminum turnings. Alkylation with propylene was effected at 160 to 170° and 200 to 600 p.s.i. over a 2.5-hr. period. The product yielded 291 g. (46%) of 2,6-diisopropyl-4-chlorophenol (b.p. 165–166.5° at 30 mm., n_D^{20} 1.5285).

Alkylation of phenol with isobutylene. A series of four reactions was carried out to demonstrate the effect of alkylation temperature upon product composition in this reaction (Table I, Exp. No. 1–4). These runs were carried out using the same molar quantities of phenol and catalyst and the gaseous olefin feed system as employed in the alkylation of phenol with propylene. In a fifth experiment (Table I, Exp. No. 5) the catalyst concentration was doubled and the experiment was carried out at atmospheric pressure in glass apparatus.

Phenyl *tert*-butyl ether was separated as the caustic insoluble portion of a fraction boiling below phenol in the fractionation of the product from Experiment No. 1. Upon redistillation, the pure ether was obtained (m.p. −24 to −25°, b.p. 90° at 32 mm., n_D^{20} 1.4881). Stevens[11] has reported a similar boiling point of 80° at 20 mm. for this compound.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.1; H, 9.33.

The physical properties of the phenolic compounds obtained in the reaction are presented in Table II. The values are in good agreement with those in the literature.[12]

TABLE II

PHYSICAL PROPERTIES OF PHENOL-ISOBUTYLENE REACTION PRODUCTS

Compound	M.P. (°C.)	B.P. (°C. at 30 mm.)
2-*tert*-Butylphenol[a]	−6.8[b]	120
4-*tert*-Butylphenol	99	138
2,6-Di-*tert*-butylphenol	36.5	147
2,4-Di-*tert*-butylphenol	57	156
2,4,6-Tri-*tert*-butylphenol	130	—

[a] n_D^{20} 1.5239, d_4^{20} 0.982. [b] An allotropic form melts at −19.2°.

Alkylation of phenol with isobutylene (optimum conditions). This experiment was carried out in an attempt to obtain a high conversion to 2,6-di-*tert*-butylphenol. The catalyst was prepared by heating 376 g. (4 moles) of anhydrous phenol and 100 ml. of toluene with 3.6 g. (0.13 formula wt.) of aluminum turnings. In this experiment the heated isobutylene feed cylinder was replaced by a weighed cylinder from which liquid isobutylene could be forced into the autoclave as desired by nitrogen pressure.

The phenol and catalyst mixture was heated to 100°. At this point 425 g. (7.6 moles) of liquid isobutylene was fed to the autoclave as rapidly as possible with sufficient cooling available to control the initial exothermic reaction. After the olefin addition was complete, the mixture was maintained at 100° to complete the reaction. The pressure in the autoclave passed through a maximum of 240 p.s.i. and finally dropped to 115 p.s.i. It is suspected that about 100 p.s.i. of the final pressure may be attributed to nitrogen dissolved in the isobutylene. The total reaction time was 7 hr. The product was processed as in the above experiments to yield 3% of recovered phenol, 9% of 2-*tert*-butylphenol, 74% of 2,6-di-*tert*-butylphenol and 9% of 2,4,6-tri-*tert*-butylphenol.

Alkylation of phenol with cyclohexene. The catalyst was prepared by heating 300 g. (3.2 moles) of phenol with 2.25 g. ($^1/_{12}$ formula wt.) of aluminum turnings. The mixture was cooled and 232 g. (3.0 moles) of cyclohexene added. The autoclave was then heated to 244° at which point an exothermic reaction was apparent and the pressure dropped from 140 to 40 p.s.i. The product was worked up to yield 83 g. (29%) of phenol, 236 g. (42%) of 2-cyclohexylphenol, 6 g. (1%) of 4-cyclohexylphenol, and 170 g. (20%) of 2,6-dicyclohexylphenol.

The 2-cyclohexylphenol (m.p. 55.5–57°, b.p. 173° at 30 mm.) gave no depression of melting point when mixed with an authentic sample of that compound. The 2,6-dicyclohexylphenol (b.p. 190° at 30 mm.) melted at 62–63.5° after recrystallization from isooctane (lit. m.p. 62–65°).[13]

Alkylation of phenol with 1-decene. The catalyst mixture was prepared from 300 g. (3.2 moles) of phenol and 4.5 g. ($^1/_6$ formula wt.) of aluminum turnings in the usual manner. The mixture was heated in the autoclave with 167 g. (1.28 moles) of 1-decene until a temperature of 300° was reached in the course of a 90-min. period. No exothermic reaction or drop in pressure was noted. The product was treated in the usual manner to yield 138 g. (49%) of "2-(2-decyl)phenol," b.p. 198–200.5° at 30 mm., n_D^{20} 1.5010. The infrared spectrum showed the presence of the hydroxyl band.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.1; H, 11.3.

Alkylation of phenol with diisobutylene. The catalyst was prepared by heating 234 g. (2.38 moles) of phenol with 4.5 g. ($^1/_6$ formula wt.) of aluminum turnings and 252 g. (2.42 moles) of diisobutylene, added after cooling. The mixture was heated to 280° over a 90-min. period with no evidence of reaction. Upon cooling, the reactor showed no residual pressure (indicating the absence of isobutylene), and distillation of the product indicated that no *tert*-butyl phenols were present. From the product was obtained 89 g. (40%) of phenol, 55 g. (11%) of 2-(1,1,3,3-tetramethylbutyl) phenol, 123 g. (25%) of 4-(1,1,3,3-tetramethylbutyl)phenol and 60 g. of higher boiling material. The *ortho*-isomer melted at 43–44° and boiled at 157–158.5° (30 mm.).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.4; H, 10.7.

The *para*-isomer melted at 85–86° (lit. m.p. 84°)[10] and boiled at 175° (30 mm.). The infrared spectra of both isomers showed the presence of the hydroxyl group.

Alkylation of 1-naphthol with propylene. The autoclave was charged with 502 g. (3.48 moles) of 1-naphthol and 2.25 g. ($^1/_{12}$ formula wt.) of aluminum turnings and an unsuccessful attempt was made to prepare the catalyst by heating to 329°. The autoclave was then cooled and 17 g. ($^1/_{12}$ mole) of aluminum isopropoxide added. The mixture was heated to 300–310° and alkylated with propylene at 600 to 700 p.s.i. over a 3-hr. period. The catalyst was hydrolyzed and removed before performing a preliminary distillation through a Vigreux column to yield 98 g. (20%) of 1-naphthol (b.p. 140–160° at 10 mm.), 374 g. of crude 2-isopropyl-1-naphthol (b.p. 160–190° at 10 mm.), and 51 g. of higher boiling materials. Refractionation of the crude 2-isopropyl-1-naphthol through a 30-plate column gave 345 g. (54%) of purified material (m.p. 45–50°, b.p. 192.5–193.5° at 30 mm.). Recrystallization from isooctane raised the melting point to 49–50°, and this material showed no melting point depression when mixed with an authentic sample[14] of 2-isopropyl-1-naphthol.

(11) Stevens, *J. Org. Chem.*, **20**, 1233 (1955).

(12) Pardee and Weinrich, *Ind. Eng. Chem.*, **36**, 596 (1944).

(13) Skraup and Beifuss, *Ber.*, **60**, 1070 (1927).

(14) Ecke and Napolitano, *J. Am. Chem. Soc.*, **77**, 6373 (1955).

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.7; H, 7.59.

Alkylation of 2-chlorophenol with isobutylene. The catalyst was prepared in the autoclave by heating 644 g. (5 moles) of 2-chlorophenol with 4.5 g. ($^1/_6$ formula wt.) of aluminum turnings. Alkylation with isobutylene was effected at 80–90° and the product worked up to give 550 g. (60%) of 2-*tert*-butyl-6-chlorophenol (b.p. 123° at 30 mm.; n_D^{20} 1.5265).

Anal. Calcd. for $C_{10}H_{13}ClO$: Cl, 19.2. Found: Cl, 19.3.

Proof of structure of 2-tert-butyl-6-chlorophenol. A portion of the product of the above experiment was chlorinated with sulfuryl chloride to yield 2,4-dichloro-6-*tert*-butylphenol (for chlorination method see under structure proof of 2,6-diisopropylphenol). The 2,4-dichloro-6-*tert*-butylphenol was obtained in 54% yield (b.p. 134° at 15 mm., n_D^{20} 1.5421).

Anal. Calcd. for $C_{10}H_{12}Cl_2O$: Cl, 32.3. Found: Cl, 32.4.

This material had physical properties and infrared spectrum identical with those of material obtained by the pyridine-catalyzed sulfuryl chloride chlorination of 2-*tert*-butylphenol.

Alkylation of 2-ethylphenol with 1-butene. The catalyst was prepared in the autoclave in the usual manner by heating 357.4 g. (2.88 moles) of 2-ethylphenol (prepared as above) with 4 g. (0.15 formula wt.) of aluminum turnings. At a temperature of 215° the reaction mixture was alkylated with 1-butene at 200–500 p.s.i. over a 3-hr. period. Working up the product in the usual manner gave 300 g. (58%) of 2-ethyl-6-*sec*-butylphenol (b.p. 140–141° at 30 mm.; n_D^{20} 1.5153).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.9; H, 10.2. Found: C, 81.1; H, 9.98.

The phenylurethan of the 2-ethyl-6-*sec*-butylphenol was prepared and found to melt at 132.5–134°.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.9; H, 7.8. Found: C, 76.5; H, 7.5.

Dealkylation of isobutylene-phenol alkylation products. A sample of phenyl *tert*-butyl ether was refluxed in a system connected to a gas bubbler. Upon boiling at atmospheric pressure for 1 hr. (liquid temperature 182°) only trace amounts of gas were evolved. Similar treatment of 2-*tert*-butylphenol (at 221–222°) and of 4-*tert*-butylphenol (at 237°) gave no evidence of gas evolution.

In order to repeat the above experiments in the presence of aluminum phenoxide, each tube was first charged with 0.01 g. of aluminum turnings and 0.5 g. of phenol. The mixture was briefly heated to effect formation of the phenoxide. To each of the three tubes was then added 5 g. of the desired compound. The tubes were then heated in an oil bath. The ether began to evolve gas at 95° and dealkylated readily at 100°. The 2-*tert*-butylphenol evolved gas rapidly at 190°. The 4-*tert*-butylphenol failed to dealkylate even when refluxed with the catalyst.

DETROIT 20, MICH.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ETHYL CORPORATION]

Base-Catalyzed Alkylation with Olefins

REX D. CLOSSON, JOHN P. NAPOLITANO, G. G. ECKE, AND ALFRED J. KOLKA[1]

Received November 19, 1956

The base catalyzed addition of very weak acids to simple olefins has been studied using the preformed sodium salts of the very weak acids as catalysts. A variety of reactants were employed, and the data are examined in regard to the mechanism of the process.

The base catalyzed addition of very weak acids to activated olefinic systems is a relatively familiar reaction as typified by the addition of alcohols, amines, and acidic hydrocarbons to acrylonitrile,[2a] butadiene,[2b] and styrene.[2c] Although the addition of very weak acids to simple olefins is a somewhat more recent development, four papers[3] and numerous patents[4] have appeared on the subject.

In several of these papers the investigators have relied upon the *in situ* formation of the sodium salt of the very weak acids, which is in reality a reaction intermediate rather than a catalyst in the process.[3b] In the present investigation the sodium salt was preformed before the alkylation step in order to assure somewhat more uniform reaction conditions. The ethylation was applied to a series of compounds including both acidic hydrocarbons and primary and secondary amines. An attempt has been made to correlate the pK_a with the reactivity of the very weak acid.

In general, the greater the pK_a of the very weak acid,[5] the lower the reaction temperature that was required to effect ethylation at a reasonable rate.

Thus cumene (relative pK_a 37)[5] and toluene are readily ethylated at temperatures of 120–140° whereas aniline (relative pK_a 27),[5] methylaniline, and *ortho*-toluidine require temperatures of 240–275°. The aliphatic amines are known to be less acidic than the aromatic amines, as evidenced by their low reactivity with sodamide, and it is found that the temperature required for their ethylation (135–160°) is lower than that required for aniline but higher than that required for toluene.

(1) Present address Koppers Co., Inc., Koppers Bldg., Pittsburgh, Pa.

(2) (a) Bruson, *Org. Reactions*, **5**, 79 (1949). (b) Wegler and Pieper, *Ber.*, **83**, 6 (1950). (c) Wegler and Pieper, *Ber.*, **83**, 1 (1950).

(3) (a) Howk, Little, Scott, and Whitman, *J. Am. Chem. Soc.*, **76**, 1899 (1954). (b) Pines, Vesely, and Ipatieff, *J. Am. Chem. Soc.*, **77**, 554 (1955). (c) Hart, *J. Am. Chem. Soc.*, **78**, 2619 (1956). (d) Pines and Mark, *J. Am. Chem. Soc.*, **78**, 4316 (1956).

(4) Whitman, U. S. Patent 2,448,641 (Sept. 7, 1948) and U. S. Patent 2,501,556 (March 21, 1950); Gresham, Brooks, and Bruner, U. S. Patent 2,501,509 (March 21, 1950); Little, U. S. Patent 2,548,803 (Apr. 10, 1951); Pines and Ipatieff, U. S. Patent 2,670,390 (Feb. 23, 1954) and U. S. Patents 2,721,885–2,721,887 (Oct. 25, 1955); Closson, Kolka, and Ligett, U. S. Patent 2,728,802 (Dec. 27, 1955), U. S. Patents 2,750,384 and 2,750,417 (June 12, 1956), and U. S. Patent 2,751,426 (June 19, 1956).

(5) McEwen, *J. Am. Chem. Soc.*, 58, 1124 (1936).

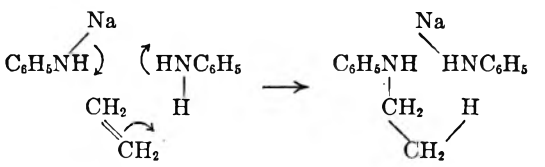
Since the strongest conjugate bases arise from the weakest acids, it is convenient to discuss this temperature correlation in terms of the base strengths of the anions participating in the first step of the ethylation. Thus anilide ion adds to ethylene (Equation 1) to yield an aliphatic carbanion, one of the strongest bases known. The greater the difference in the basicities of the two anions, the higher the temperature that will usually be required to effect ethylation.

(1) $C_6H_5NH^- + CH_2{=}CH_2 \rightleftharpoons C_6H_5NHCH_2CH_2^-$

The carbanion produced in (Equation 1) might be expected to have a short life at the temperature employed in the alkylations. It may loose a hydrogen to produce sodium hydride, it may undergo fission to the parent anion and olefin, it occasionally will add to a second molecule of ethylene, or more commonly it may acquire a proton from a molecule of the very weak acid being alkylated (Equation 2). The possibility of a concerted process should

(2) $C_6H_5NHCH_2CH_2^- + C_6H_5NH_2 \longrightarrow C_6H_5NHC_2H_5 + C_6H_5NH^-$

possibly be considered (Equation 3).



The failure of aniline to undergo dialkylation to a major extent is probably to be associated both with the fact that anilide ion is a weaker base than *N*-ethylanilide ion, and to the fact that the ethylation is a reversible process. An attempt to ethylate *N*-ethylaniline resulted both in partial fission to ethylene and aniline, and also yielded a small amount of *N*-*n*-butylaniline. The abstraction of a proton from the ethyl group to yield the *β*-*N*-ethylaniline carbanion would appear requisite to the production of such compounds.

Steric factors can play an appreciable role in the base-catalyzed alkylation reaction. Thus cumene required a somewhat higher temperature for alkylation than did toluene, whereas tetralin was readily ethylated twenty degrees lower than toluene. Similarly piperidine was ethylated some thirty degrees lower than dibutylamine. Although 2-methyl-6-ethylaniline readily formed the *N*-sodio catalyst, attempts at ethylation were unsuccessful, and this behavior is likely the result of steric hindrance.

An amide ion displacement reaction was observed to occur between certain amines and *N*-sodio amines. Sodium anilide reacted with hexylamine to yield *N*-hexylaniline:

$$C_6H_5NH^- + C_6H_{13}NH_2 \longrightarrow C_6H_5NHC_6H_{13} + NH_2^-$$

$$C_6H_5NH_2 + NH_2^- \longrightarrow C_6H_5NH^- + NH_3$$

Since sodamide reacts with aniline to form sodium anilide, the process should be a catalytic one and require only a catalytic amount of sodium anilide. A second type of this reaction represented by the reaction of hexylamine with *N*-sodiohexylamine to yield dihexylamine and amide ion, might be expected to be stoichiometric with the amount of *N*-sodiohexylamine used.

The use of higher olefins in the base catalyzed alkylation reaction does not appear promising in view of their sluggish behavior.

EXPERIMENTAL

All liquid reagents were dried by azeotropic distillation before use. Reactive intermediates were protected from moisture and air by handling under a nitrogen atmosphere. Melting and boiling points are uncorrected except where otherwise stated.

Ethylation of aniline. The catalyst was prepared by adding 19.5 g. (0.5 mole) of sodamide to 300 ml. of aniline and slowly heating to 180° to insure complete ammonia evolution. The mixture was charged to a 2-l. steel autoclave along with an additional 300 ml. of aniline (600 g., 6.45 moles total). The solution was heated to 150° at which point the autoclave was pressured to 400 p.s.i. with ethylene. Heating was then continued and a drop in pressure noted when 270° was reached. The reaction mixture was maintained at 275° and under ethylene pressures of 600–800 p.s.i. for a 6-hr. period.

After cooling, the catalyst was destroyed by the addition of 200 ml. of water. The product was washed with water, dried by azeotropic distillation with toluene, and fractionally distilled. The following products were obtained: aniline (106 g., 18%), *N*-ethylaniline (588 g., 75%), *N*,*N*-diethylaniline (24 g., 2%), and a higher boiling residue (23 g.). The structures of the products were determined by their physical properties and by comparison of their infrared spectra with those of authentic samples.

Ethylation of o-toluidine. The reaction was carried out in the same manner as the above experiment, except that ethylene absorption occurred at 240°. The product consisted of unreacted 2-methylaniline and *N*-ethyl-2-methylaniline (206 g., 27%; b.p. 212–212.5°; n_D^{20} 1.5469).

Attempted ethylation of 2-methyl-6-ethylaniline. This experiment was carried out in the manner of the above reactions; however, the use of reaction temperatures of up to 322° failed to produce any evidence of ethylene absorption. The product consisted solely of recovered 2-methyl-6-ethylaniline.

Ethylation of N-methylaniline. The catalyst was prepared by the reaction of 18 g. (0.5 mole) of sodamide with 585 g. (5.48 moles) of *N*-methylaniline. Ethylation was effected over a 4.5-hr. period at 250–255° and 600–800 p.s.i. The product was worked up to yield 171 g. (29%) of *N*-methylaniline and 389 g. (53%) of *N*-methyl-*N*-ethylaniline. The *N*-methyl-*N*-ethylaniline (b.p. 202.5°; n_D^{20} 1.5476) yielded a picrate melting at 128–129° (lit. 128–131°[6]).

Attempted ethylation of N-ethylaniline. The catalyst was prepared from 19.5 g. (0.5 mole) of sodamide and 575 g. (4.75 moles) of *N*-ethylaniline. The mixture was heated in the autoclave to 150° and ethylene added to 400 p.s.i. pressure. Upon further heating to 290°, the pressure increased to 640 p.s.i. with no evidence of ethylene absorption. The product was worked up in the usual manner to yield 63 g. (14%) of aniline, 410 g. (71%) of *N*-ethylaniline, 8 g. (1%) of *N*-butylaniline, and 18 g. of residue. The *N*-butylaniline was identified by its physical properties (b.p. 127–128° at 20 mm.; n_D^{20} 1.5379) and by the preparation of its

(6) Wittig and Merkle, *Ber.*, **76B**, 109 (1943).

meta-nitrobenzene sulfonyl derivative (m.p. and mixed m.p. 92–93°). No evidence of *N,N*-diethylaniline was found.

In order to demonstrate that no decomposition had occurred during the preparation of the catalyst, *N*-sodio-*N*-ethylaniline was prepared as above. Upon hydrolysis and fractionation only *N*-ethylaniline was obtained.

Alkylation of aniline with propylene. The autoclave charge was identical to that used in the ethylation of aniline. The mixture was heated to 200° and the autoclave pressured to 360 p.s.i. with propylene. Alkylation was effected at 330° and 700 p.s.i. over a 30-min. period after which no further pressure drop was evident. The product was worked up to yield 470 g. (78%) of aniline, 56 g. (6%) of *N*-isopropylaniline, and a 17 g. residue. The *N*-isopropylaniline (b.p. 201.5–203°; n_D^{20} 1.5394) yielded an acetyl derivative melting at 41–42° (lit.[7] m.p. 42°).

Ethylation of dibutylamine. The *N*-sodio-dibutylamine catalyst was prepared using the method employed by Danforth.[8] Butadiene (10 g., 0.18 mole) was bubbled into a stirred dispersion of 11 g. (0.48 mole) of sodium in 400 ml. of dibutylamine at 10°. This mixture along with an additional 200 ml. of dibutylamine (456 g., 3.52 moles total) was charged to the autoclave. Ethylation was carried out at 132–135° over a 5-hr. period using ethylene pressures of 300–800 p.s.i. The catalyst was hydrolyzed and the product fractionated to yield 35 g. (8%) of dibutylamine and 354 g. (63%) of *N*-ethyldibutylamine (b.p. 177.5–178°; n_D^{20} 1.4221).

Ethylation of piperidine. In the case of piperidine it was found that the presence of a few percent of pyridine (which could not be removed from the piperidine) rendered the use of butadiene unnecessary in the preparation of the catalyst. The autoclave was charged with a dispersion of 3.5 g. (0.15 mole) of sodium in 425 g. (5 moles) of piperidine. Ethylation was effected over a 3-hr. period at 97–100° and 600–750 p.s.i. The product was found to consist of 43 g. (10%) of piperidine, 446 g. (80%) of *N*-ethylpiperidine, and 28 g. of residue. The *N*-ethylpiperidine boiled at 129°; n_D^{20} 1.4431. The picrate was prepared and found to melt at 168° (lit. 165–166°[9]).

Ethylation of hexylamine. The autoclave charge was prepared from 500 g. (4.93 moles) of hexylamine and 11 g. (0.48 mole) of sodium using the butadiene technique as in the dibutylamine alkylation. Ethylation was effected over a 1-hr. period at 150–160° and 400–600 p.s.i. There were obtained 140 g. (28%) of hexylamine, 190 g. (38%) of *N*-ethylhexylamine, 76 g. (10%) of *N*-hexyldiethylamine, and 58 g. (13%) of dihexylamine. The *N*-ethylhexylamine boiled at 159°; n_D^{20} 1.4206, and the *N*-hexyldiethylamine boiled at 179.5°. The dihexylamine (b.p. 75° at 1 mm.; n_D^{20} 1.4339) had the physical properties and infrared spectrum identical with those of an authentic sample prepared by the reaction of hexylamine and hexyl chloride.

Reaction of hexylamine with N-sodiohexylamine. Using the butadiene method described in the dibutylamine ethylation, 7 g. (0.3 mole) of sodium was reacted with 422 g. (4.15 moles) of hexylamine. The mixture was heated in the autoclave under a nitrogen atmosphere at 165° for 2 hr. The product was hydrolyzed and fractionated to yield 310 g. (73%) of hexylamine and 39 g. (10%) of dihexylamine (b.p. 63–68° at 0.5–1 mm.; n_D^{20} 1.4333).

Reaction of hexylamine and sodium anilide. A solution of sodium anilide in aniline was prepared by heating 18 g. (0.5 mole) of sodamide and 400 ml. of aniline to 180°. This solution together with an additional 150 ml. of aniline (5.9 moles total) was charged to the autoclave and 152 g. (1.5 moles) of hexylamine added. The mixture was heated at 330° for 2 hr. and a 200 p.s.i. increase in pressure noted. The product was worked up to yield 478 g. (88%) of aniline, 46 g. (30%) of hexylamine, 50 g. (19%) of *N*-hexylaniline, and 28 g. of residue. The *N*-hexylaniline boiled at 156–168° at 20 mm.; n_D^{20} 1.5218.

Anal. Calcd. for $C_{12}H_{18}N$: N, 7.9. Found: N, 8.1.

The physical properties and infrared spectrum of this material were identical with those of an authentic sample prepared from the reaction of aniline with hexyl bromide.

Ethylation of toluene. The preparation of the benzylsodium catalyst was effected using 11.5 g. (0.5 mole) of sodium, 28.2 g. (0.25 mole) of chlorobenzene, and 300 ml. of toluene.[10] The mixture was charged to the autoclave together with an additional 300 ml. of toluene. Ethylation was carried out at 125–130° at pressures of 300–800 p.s.i. over a 4-hr. period. The reaction was highly exothermic, and relatively low ethylene pressures were used in the early stages of the reaction. The catalyst was hydrolyzed by the addition of ethanol, and the product was washed and fractionated. There were obtained 7 g. (1%) of toluene, 179 g. (27%) of *n*-propylbenzene, 549 g. (66%) of 3-phenylpentane, and 15 g. of residue. The *n*-propylbenzene (b.p. 158.5°; n_D^{20} 1.4914) and the 3-phenylpentane (b.p. 187.5; n_D^{20} 1.4882) had been previously reported from the ethylation of toluene.[3b]

Ethylation of cumene. Amyl sodium was prepared by a method similar to that described in the literature.[11] To a dispersion of 23 g. (1 mole) of sodium in 200 ml. of heptane and 100 ml. of octane was added 53 g. (0.5 mole) of 1-chloropentane. High speed stirring was used and the mixture was maintained at −5 to 5° during the 40-min. addition period. To the amyl sodium prepared in this manner was added 300 ml. of cumene at 10°, and the mixture let stand at room temperature overnight. The catalyst mixture together with an additional 650 ml. (6.85 moles total) of cumene was charged to the autoclave and reacted with ethylene at 140°. The ethylation was effected using ethylene pressures of 450–600 p.s.i. over a 90-min. period. The product yielded 346 g. (34%) of *tert*-amylbenzene (b.p. 188.5°; n_D^{20} 1.4970), which was identified by comparison of its infrared spectrum with that of an authentic sample of *tert*-amylbenzene.[12]

The compound was previously reported by the ethylation of cumene with ethylene using sodium promoted with anthracene as a catalyst.[3b]

Alkylation of toluene with propylene.[3d] The autoclave charge, consisting of benzylsodium and toluene, was identical with that used in the ethylation of toluene. Reaction with propylene occurred slowly at 185–188° and 700–800 p.s.i. The product was hydrolyzed and fractionated to yield 425 g. (76%) of toluene and 47 g. (6%) of isobutylbenzene. The isobutylbenzene (b.p. 170.5–171°; d_4^{20} 0.853; n_D^{20} 1.4863) was identified by its physical properties and by comparison of its infrared spectrum with that of an authentic sample.

Ethylation of tetralin. The α-sodio tetralin catalyst was prepared in the same manner as benzylsodium using tetralin in place of toluene. Interchange of the phenylsodium and tetralin was effected by heating at 60–80° for 3 hr. The ethylation was carried out at 140° and 600–700 p.s.i. over a 6-hr. period. There were obtained 4% of recovered tetralin, 21% of 1-ethyltetralin, 41% of 1,4-diethyltetralin, and 8% of a compound believed to be 1,1,4-triethyltetralin. The 1-ethyltetralin boiled at 239.9° (corr.); n_D^{20} 1.5320 (lit.[13] b.p. 239.4°; n_D^{20} 1.5316). The 1,4-diethyltetralin boiled at 261°; n_D^{20} 1.5262.

Anal. Calcd. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.3; H, 10.7.

The structure of the 1,4-diethyltetralin was established by dehydrogenation. A 1.0 g. sample was heated with 0.34 g. of sulfur at 250° for 10 min. The product was distilled at 90–

(7) Hickinbottom, *J. Chem. Soc.*, 994 (1930).

(8) Danforth, U. S. Patent 2,527,709 (Oct. 31, 1950); *Chem. Abstr.*, 45, 3870 (1951).

(9) Winans and Adkins, *J. Am. Chem. Soc.*, 54, 310 (1932).

(10) Gilman, Pacevitz, and Baine, *J. Am. Chem. Soc.*, 62, 1517 (1940).

(11) Morton, Massengale, and Brown, *J. Am. Chem. Soc.*, 67, 1620 (1945).

(12) The authors are indebted to Dr. John Derfer of API Project 45 for this authentic spectrum.

(13) Hipsher and Wise, *J. Am. Chem. Soc.*, 76, 1747 (1954).

100° at 1 mm. A picrate melting at 90.5–92.5° was prepared from the distillate. The literature[14] reports the picrate of 1,4-diethylnaphthalene to melt at 91–93°.

The material believed to be 1,1,4-triethyltetralin boiled at 174° at 50 mm; n_D^{20} 1.5236.

(14) Arnold and Barnes, *J. Am. Chem. Soc.*, 66, 960 (1944).

Anal. Calcd. for $C_{16}H_{24}$: C, 88.89; H, 11.11. Found: C, 88.9; H, 11.2.

Acknowledgment. The authors wish to express their appreciation to Dr. Waldo B. Ligett for his helpful suggestions and continued interest during the course of this work.

DETROIT 20, MICH.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, AIR REDUCTION CO., INC.]

Sodium Acetylide. I. Preparation of Sodium Acetylide by Reaction of Acetylene with Sodium in Organic Media

T. F. RUTLEDGE

Received December 5, 1956

A procedure for preparing sodium acetylide in organic diluents is described. Sodium metal, as a dispersion, is reacted with acetylene at atmospheric pressure and at a critical temperature. Acetylene purity is extremely important. Dry, stable, finely divided sodium acetylide is described.

The preparation of sodium acetylide in liquid ammonia is a well-known reaction.[1] Liquid ammonia is relatively difficult to handle, and accordingly it has not been used extensively for large scale work. Although a fairly pure sodium acetylide can be prepared in liquid ammonia, attempts to isolate dry sodium acetylide from this reaction medium have been reported to be somewhat hazardous.[2] Experience in this laboratory confirmed a literature report[3] that sodium acetylide prepared in liquid ammonia could not be placed in inert organic diluents to form a finely divided suspension. A coarse, dark, and somewhat hard solid resulted in most cases.

Sodio derivatives of monosubstituted acetylenes are prepared readily in organic diluents such as benzene and ether.[4,5] Acetylene reacts with sodium metal in organic diluents with great difficulty. One of the few references found is a German patent[6] which describes preparation of sodium acetylide by passing acetylene into a stirred mixture of sodium and xylene at reflux temperature (about 135–140°). The product was stated to be a yellowish-white powder, the sodium acetylide content of which corresponded to 83% yield. Although no reaction time was mentioned, a time of more than 60 hours was apparently required. This is inferred from a statement contained in a later German patent,[7] which claims faster production of sodium acetylide by reaction of acetylene with sodium deposited on sand. It is interesting to note that in 1897 Matignon[8] described a process for preparing sodium acetylide which is almost identical to that described in the patent.[7]

Since sodium acetylide is an important intermediate in the practice of acetylene chemistry, it appeared desirable to find a method for fast and easy preparation of this material in organic diluents. A stable, dry powder of good purity should be valuable as a reagent.

DISCUSSION OF RESULTS

When sodium metal of 10–25 micron particle size was suspended in xylene and subsequently treated with pure acetylene at various temperatures, optimum reaction was obtained at 100–110°. The course of the reaction was followed by means of a hydrogen analyzer attached to the exit end of the reactor.[9] Complete reaction of 0.25 mole of sodium in 300 ml. of xylene required 1.5 to 2.5 hours. Yield of sodium acetylide based on sodium was virtually quantitative. Yield based on acetylene was 75–85%.

The data in Table I summarize experiments which demonstrate the effect of reaction tempera-

(1) T. H. Vaughn, U. S. Patent 2,198,236, April 23, 1940. E. A. Bried and G. F. Hennion, *J. Am. Chem. Soc.*, 59, 1310 (1937). T. H. Vaughn, G. F. Hennion, R. R. Vogt, and J. A. Nieuwland, *J. Org. Chem.*, 2, 1 (1937). P. Pomerantz, A. Fookson, T. W. Mears, S. Rothberg, and F. L. Howard, *J. Res. Nat'l Bur. Standards*, 52, 51 (1954).

(2) Private communications from J. H. Wotiz and M. S. Newman.

(3) G. F. Hennion and E. P. Bell, *J. Am. Chem. Soc.*, 65, 1847 (1943).

(4) J. R. Johnson, A. M. Schwartz, and T. L. Jacobs, *J. Am. Chem. Soc.*, 60, 1882 (1938). H. Gilman and R. V. Young, *J. Org. Chem.*, 1, 315 (1936).

(5) P. Ivitsky, *Bull. soc. chim. France*, 35, 357 (1924).

(6) O. Ernst and O. Nicodemus, German Patent 494,575, Nov. 21, 1926.

(7) W. Schulenberg, German Patent 535,071, Feb. 8, 1929.

(8) C. Matignon, *Compt. rend.*, 124, 775 (1897).

(9) Use of a hydrogen analyzer for this purpose was suggested by Dr. A. J. Buselli of this laboratory. This proved to be the best method of following the course of the reaction. Dr. Buselli contributed other valuable suggestions prior to and during the conduct of the work.

TABLE I

PREPARATION OF SODIUM ACETYLIDE IN ORGANIC DILUENTS
(Sodium, 0.25 Moles, in 300 cc. Diluent)

Run	Diluent	Temp., °C.	Reaction Time, Hrs.	Yield[a] Sodium Acetylide (on Sodium), %
1	Xylene	100–105	2.5	99+
2	Xylene	118–120	2.75	71.5
3	Xylene	130–135	3	7.3
4	Di-*n*-butyl Carbitol	60–70	2.5	99+
5	Di-*n*-butyl Carbitol	90–100	1	99+
6	Di-*n*-butyl Carbitol	100–110	0.75	99+
7	Di-*n*-butyl Carbitol	130	3.33	59
8	Di-*n*-butyl Carbitol	145–150	1.5	49
9	Di-*n*-butyl Carbitol	160–165	3	32
10	Di-*n*-butyl Carbitol	175–180	1.25	31
11	Di-*n*-butyl Ether	75–85	2	99+
12	Di-*n*-butyl Ether	100–105	1	99+
13	Dioxane	65–70	2	99+

[a] Yield = $\frac{\text{moles sodium acetylide formed}}{\text{moles sodium consumed}} \times 100$. Sodium was consumed completely in every case.

ture on reaction time and yield. Use of several diluents is illustrated.

When xylene was the diluent (Runs 1–3) there was very striking decrease in yield of acetylide as the reaction temperature was increased from 100° to 130°. The decrease in yield was less pronounced in the case of di-*n*-butyl carbitol (Runs 4–10). In three of the diluents (Runs 4, 11, 13) excellent reactions were obtained at temperatures well below the melting point of sodium metal (97.5°). Excellent reaction occurred in dioxane at 65–70°. Attempts to prepare the pure acetylide in dioxane at temperatures below or above this range were not successful. This temperature range for dioxane was the narrowest and most critical encountered in the present work. Numerous other diluents have been utilized, optimum reaction temperature being determined as described in the Experimental Part.

Several experiments demonstrated that sodium particle size below approximately 100 microns is desirable. In two different diluents (xylene and di-*n*-butyl carbitol) use of sodium sand (about 100 microns) resulted in reaction times almost double those shown in Table I, and in yields of only about 50%.

Since commercial, or even C.P., grade sodium metal contains impurities inside the chunks or pieces, it was desirable to purify the metal before use. A simple melting procedure separated enough of the impurities to result in sodium acetylide of 98–99% purity. Unpurified sodium usually resulted in an acetylide of 95–96% purity. Sodium carbonate was the chief impurity found. When acetylene is removed from a commercial cylinder, the chief contaminant is acetone, along with trace amounts of phosphine, vinyl sulfide, arsine, and ammonia. It was found that this grade of acetylene required further purification. Acetone was a "poison" for the reaction. The trace quantities of the other contaminants were also deleterious. Numerous purification systems were investigated. Activated alumina proved to be the most efficient and convenient purification medium for laboratory work. A simple test (2,4-dinitrophenylhydrazine for acetone) was applied to the gas through the train to establish when the adsorbent required regeneration. Regeneration was accomplished by treatment with steam and/or hot air (200–300°).

Oxygen was found to be a potent "poison" for the reaction. Oxygen, particularly along with the trace impurities mentioned above, caused either very long reaction times (up to 18 hours), or no reaction at all. A maximum oxygen level of about 0.3 volume % was maintained for best reactions. This was easily accomplished, since traces of oxygen (in air) contained in commercial acetylene cylinders can be removed by "bleeding" off a few pounds of pressure from the gas phase of the cylinder. The air is reduced to a negligible amount very quickly, and the remainder of the acetylene in the cylinder can be used without difficulty. Exclusion of air from the reactor was also found to be essential.

Probably related to this effect of oxygen was the observation that sodium "dispersions" stabilized with cumene hydroperoxide failed to react with acetylene. Normal reactions could be obtained by adding hydroquinone to the dispersion before addition of acetylene. Hydroquinone did not alter the poisoning effect of oxygen, however. It was deduced from this fact that oxygen does not inhibit the reaction *via* an organic hydroperoxide.

Xylene and di-*n*-butyl ether were satisfactory as diluents after a simple drying operation. Dioxane and the polyether diluents required more careful purification (sodium or sodium hydroxide), and therefore were also distilled from sodium.

Sodium acetylide prepared in diluents such as xylene, dioxane, and butyl ether was separated as a stable, dry, palpable powder. The diluent was removed by filtration followed by pumping at 65–70° and 5 mm. pressure. Alternatively, the filtered acetylide was purged with acetylene at 100–125° for complete removal of residual diluent. It was found that the sodium acetylide adsorbed about 2.2 times its own weight of xylene, about twice its weight of butyl ether, and about 1.6 times its weight of dioxane. As expected, xylene removal was more time-consuming and difficult than was removal of butyl ether or dioxane.

The powdered acetylide, very slightly yellow to gray-white in color, was relatively stable. It could be heated to about 300° in the absence of air. Although no explosion or rapid evolution of gas occurred, the darkening of color to brown indicated probable disproportionation to sodium carbide. At 170–190° in air, a slow ignition and smooth burning occurred. At 215–235° in air, flash ignition and quiet burning was noted. The powder could be poured into a large excess of water without flashing or burning. Vigorous evolution of acetylene occurred. The material resembled powdered calcium carbide in this respect. Treatment of a large quantity of the powder with a small amount of water in the presence of air was uneventful below about 125°. Above this temperature a drop of water caused charring, glowing, and ultimately, vigorous burning of the acetylide. The acetylide was not shock sensitive. Pounding and scraping between surfaces of steel, wood, and asphalt tile in all combinations failed to cause any ignition or detonation. The storage stability of the substance was excellent. One sample was stored in the absence of air for over a year without detectable change in composition. A very slight yellowing was noted. After a year's storage, the powder was usable and reactive.

Literally hundreds of samples of sodium acetylide have been prepared in our laboratory. Many have been dried, and used subsequently in another diluent. The material resuspended quickly and easily, and suffered no loss of reactivity due to drying. The powdered acetylide prepared by this procedure was soluble in ammonia. It reacted as well as ordinary acetylide prepared in ammonia.

Examined under a microscope, the acetylide before diluent removal was in the form of spheres of the same size as the particles of sodium originally used. After diluent removal, the particles were irregular in shape, and smaller (5–15 microns) than the original sodium particles. Sodium acetylide prepared in dioxane appeared to be small spheres or circles. Numerous lines radiated from the center like spokes in a wheel. Some of the particles were small segments of a circle, half circles, etc. Here a definite crystalline form appeared probable.

Some reactions utilizing this type of sodium acetylide will be described in subsequent publications.

EXPERIMENTAL

Sodium metal (400 g.) was purified by melting under xylene in a 2 l. separatory funnel heated by means of a mantle or heating tape. The molten metal was stirred gently and the nonmetallic impurities floated to the surface of the sodium. The stopcock was then heated by means of an infrared lamp, and the sodium drained into 400 g. of dry xylene (purified or technical grade). Care was exercised to avoid nonmetallic impurities.

Preparation of sodium dispersions. Fifty wt. % "dispersions" of 10–25 micron particle size were prepared according to known methods with three different types of apparatus.[10,11] As stabilizer and dispersing agent, aluminum stearate (0.25 wt. % on sodium) and oleic acid (0.5 wt. % on sodium) were added rapidly after stirring or pumping for 3–5 minutes.

Preparation of sodium acetylide. A 1-liter, three-necked flask equipped with a crescent-blade stirrer, electric stirring motor, reflux condenser, thermometer, and a gas inlet tube (ending below the liquid surface) served as the reactor. Commercial cylinder acetylene (Airco) was passed through a stainless steel wet test meter, thence through two towers filled with 8–14 mesh activated alumina. Total weight of alumina was about 550 g. This alumina purified about 2.4 l. of acetylene per gram. Deactivation was accompanied by a yellow color in the absorbent bed, and by a positive test for acetone in the effluent gas. The exit end of the water-cooled condenser was connected *via* a trap cooled with Dry Ice to a thermal conductivity cell calibrated for direct reading of percent hydrogen in acetylene.

Xylene (300–400 ml.) was placed in the reaction vessel, and the entire apparatus flushed thoroughly with dry nitrogen to remove moisture and air. Sodium "dispersion" (0.25 mole of sodium) was added quickly, and the mixture heated to reaction temperature while stirring. Acetylene was then introduced at a rate sufficient to maintain saturation. After about 1.5 hr., the reaction mixture became gray-white (*via* a black stage), and hydrogen evolution ceased. Acetylene was then discontinued.

Isolation of dry sodium acetylide. After the reaction mixture had settled for several hours, about half the xylene was removed by decantation or pipetting. The slurry was transferred (N_2 atmosphere) into a 1/2 liter, round bottom flask equipped with a plug containing a stopcock. The flask was inverted, and excess xylene filtered off through a glass wool plug or fritted glass disc. The flask was then placed upright in an oil bath held at 65–70°, and a vacuum of 5 mm. Hg applied. Pumping was continued until the dry powder reached a constant weight (usually 2–4 hours). Excessively long treatment caused some disproportionation to sodium carbide and acetylene.

Stability tests. Thermal stability was determined on an electrically heated melting point block. Samples were uncovered for access to air, and covered for determination of stability in the absence of air.

Analytical procedure. This procedure was developed by L. Barnes, Jr., L. J. Molinini, J. A. Puglisi, and Miss N. F. Hamilton of the Analytical Department of this laboratory. Their cooperation and assistance are gratefully acknowledged.

A sample (0.2–0.4 g.) was weighed into a stoppered vial in a dry-box under an atmosphere of dry nitrogen. The vial was placed in a 500 ml. suction flask, equipped with a glass tube with a stopcock on the side arm, and vacuum applied until the stopper was forced off the vial. The side arm of the flask was connected *via* a piece of glass tubing into a vessel containing 100–150 ml. of distilled water. The stopcock was opened, and the water drained into the flask. After shaking and thorough mixing (a), the alkaline solution was quickly titrated with 0.1*N* HCl to the phenolphthalein end point. (b) A few drops of methyl purple were added, and the titration continued to the end point.

$$\text{Titration (a) Free alkalinity } \frac{\text{meq.}}{\text{g.}} = \frac{\text{ml. HCl} \times N}{\text{Sample (g.)}}$$

$$\text{Titration (b) Carbonate alkalinity } \frac{\text{meq.}}{\text{g.}} = \frac{\text{ml. HCl} \times N}{\text{Sample (g.)}}$$

(c) Acetylenic hydrogen was determined as above, with a second sample of acetylide, except slaking liquid was 5% aqueous silver nitrate. A total of 100 ml. was allowed to

(10) Technical Promotion, Sodium Dispersions, National Distillers Chemical Company, 1953, pp. 8–9, 10–11.

(11) Stir-O-Vac unit, Labline, Inc., Chicago, Ill.

enter the flask, and the contents were shaken vigorously for 3–5 minutes. Liberated nitric acid was titrated to the methyl purple end point with 0.1*N* NaOH.

$$\text{Titration (c) Acidity meq./g.} = \frac{\text{ml. NaOH} \times N}{\text{Sample (g.)}}$$

$$\text{Thus: \% Sodium acetylide} = \frac{(a + b + c) \times 100}{2 \times 20.83}$$

$$\text{\% Sodium carbonate} = \frac{2b}{18.86} \times 100$$

$$\text{Free alkalinity as \% Na} = \frac{a - \left(b - \frac{a + b + c}{2}\right)}{43.48} \times 100$$

Acknowledgment. The author gratefully acknowledges the contributions of G. L. Moore, R. L. Siegmann, and T. E. Johnson, who performed a prodigious amount of experimental work, and wishes to thank B. C. Redmon, E. R. Blanchard, and A. M. Lyon for valuable suggestions and for encouragement to publish this work.

MURRAY HILL, N. J.

[CONTRIBUTION FROM THE INSTITUTE OF CHEMISTRY, FACULTY OF SCIENCES, BELGRADE, AND THE INSTITUTE OF CHEMISTRY, BELGRADE]

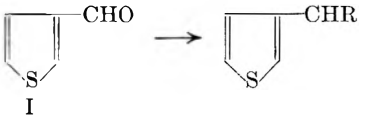
Chemistry of Thiophene. I. Derivatives of 3-Thiophenecarboxaldehyde

MIHAILO LJ. MIHAILOVIĆ[1] AND MARGITA TOT

Received November 14, 1956

The preparation of several new derivatives of 3-thiophenecarboxaldehyde is described.

3-Thiophenecarboxaldehyde (I), which was practically unknown until 1948 when Campaigne and LeSuer[2] developed a convenient method for its preparation, starting from 3-methylthiophene through 3-thenyl bromide, so far has been studied only to a limited extent. However, many derivatives of this aldehyde might be of interest as starting products for various syntheses of 3-substituted thiophene compounds. In this paper are described the preparations of several derivatives of 3-thiophenecarboxaldehyde, which were carried out by applying some typical aromatic aldehyde condensations.



I

II, R = $(NHCOCH_3)_2$; III, R = $(NHCOC_6H_5)_2$
IV, R = NC_6H_4OH-*p*; V, R = $CHCOC_6H_5$
VI, R = $C(CO)C{=}CHC_4H_3S$; VII, R = $C(C_6H_5)CN$

VIII, R = $CHCOOH$; IX, R = CH_2CH_2COOH

X, R = $CH(CH_2(COOH)_2)$

3-Thiophenecarboxaldehyde (I) reacted with benzamide or acetamide in acetic anhydride to yield the corresponding well crystallized *N,N'*-(3-thenylidene)bisamides (II and III). Bisamides, in general, can be used for the characterization of aldehydes;[3] besides they react with most compounds containing active hydrogen atoms giving unsaturated or acylamino compounds.[4]

With *p*-aminophenol, 3-thiophenecarboxaldehyde (I) gave the corresponding Schiff base IV. In alkaline solution, I reacted with acetophenone to yield the α,β-unsaturated ketone V. The condensation of cyclohexanone with two molecules of 3-thiophenecarboxaldehyde afforded 2,6-dithenylidenecyclohexanone (VI). From I and phenylacetonitrile, in the presence of sodium methoxide, α-phenyl-β-(3-thienyl)acrylonitrile (VII) was obtained.

The Doebner modification of the Perkin reaction with malonic acid in the presence of pyridine and piperidine gave very good yields of 3-(3-thienyl)-acrylic acid (VIII). Upon reduction of VIII with sodium-amalgam, by the usual procedure, 3-(3-thienyl)propionic acid (IX) was obtained. The same acid has been previously prepared by Campaigne and McCarthy[5] from 3-thenylmalonic acid (X). If the condensation of I with malonic acid was carried out in ethanolic ammonia at 70–75°, with subsequent reduction with sodium-amalgam in the presence of carbon dioxide,[6] 3-thenylmalonic acid (X) was obtained, in 72% yield. Esterification of X with ethanol afforded the corresponding diethyl ester. Both the acid X and its ester have been previ-

(1) Requests for reprints should be addressed to Dr. M. Lj. Mihailović, Institute of Chemistry, Faculty of Sciences, 1, Studentski trg, Belgrade, Yugoslavia.

(2) Campaigne and LeSuer, *J. Am. Chem. Soc.*, **70**, 1555 (1948); Campaigne, Bourgeois, and McCarthy, *Org. Syntheses*, **33**, 93 (1953).

(3) Stefanović, Bojanović, and Vandjel, *Bull. soc. chim. Belgrade*, **18**, 579 (1953); Stefanović, Mihailović, Bojanović, and Vandjel, *Bull. soc. chim. Belgrade*, **20**, 417 (1955).

(4) Stefanović and Stefanović, *J. Org. Chem.*, **21**, 161 (1956). This communication contains references to previous papers about reactions of bisamides.

(5) Campaigne and McCarthy, *J. Am. Chem. Soc.*, **76**, 4466 (1954).

(6) Owen and Nord, *J. Org. Chem.*, **15**, 988 (1950).

ously synthesized by another route:[5,7] diethyl malonate and 3-thenylbromide reacted to give the diethyl ester of X, which upon saponification was converted to 3-thenylmalonic acid (X).

Campaigne *et al.*[8] have reported the formation of 3-thiophenecarboxaldehyde thiosemicarbazone, melting at 151–152°. However, the thiosemicarbazone that we prepared from 3-thiophenecarboxaldehyde and thiosemicarbazide, in the cold, crystallized in white needles, m.p. 160°. Upon standing it turned yellow.

EXPERIMENTAL[9,10]

N,N'-(3-Thenylidene)bisbenzamide (III). A mixture of 1.12 g. (0.01 mole) of 3-thiophenecarboxaldehyde,[2] 3.63 g. (0.03 mole) of benzamide, and 2.5 ml. of acetic anhydride was heated on the water bath for 4 hr. The reaction mixture was cooled in ice and the white crystalline solid that separated was filtered and washed with small amounts of cold diethyl ether. There was obtained 1.72 g. (51.2%) of bisamide III, m.p. 213°. Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_{19}H_{16}N_2O_2S$: N, 8.33. Found: N, 8.19.

N,N'-(3-Thenylidene)bisacetamide (II). A mixture of 1.12 g. (0.01 mole) of 3-thiophenecarboxaldehyde, 2.36 g. (0.04 mole) of acetamide, and 1 ml. of acetic anhydride was treated as above. The crude bisacetamide II, m.p. 228°, was obtained in a yield of 61.3% (1.3 g.). After 3 crystallizations from acetone the product melted at 231°.

Anal. Calcd. for $C_9H_{12}N_2O_2S$: N, 13.19. Found: N, 13.30.

p-(3-Thenylideneamino)phenol (IV). In a three-necked flask fitted with a mercury sealed mechanical stirrer and a reflux condenser were placed 16 ml. of ethanol and 2.18 g. (0.02 mole) of *p*-aminophenol. The mixture was heated to boiling and 2.24 g. (0.02 mole) of 3-thiophenecarboxaldehyde was added in small portions, during 15 min. The mixture was then stirred for another 20 min., but without heating. After standing for 5 hr. at −5°, the brown crystalline precipitate was separated by filtration and washed with cold 50% ethanol. There was obtained 1.75 g. (43.1%) of crude IV, m.p. 197°. Treatment with decolorizing charcoal and 2 crystallizations from ethanol afforded drab needles, m.p. 202.5°.

Anal. Calcd. for $C_{11}H_9NOS$: C, 64.99; H, 4.46; N, 6.89. Found: C, 65.18; H, 4.58; N, 7.03.

1-Phenyl-3-(3-thienyl)-2-propene-1-one (V). To a solution of 1.0 g. (0.025 mole) of sodium hydroxide in 9.3 ml. of water and 4.6 ml. of ethanol, 2.4 g. (0.02 mole) of acetophenone and 2.24 g. (0.02 mole) of 3-thiophenecarboxaldehyde were added with stirring. The temperature, during the addition, was maintained by external cooling at 10–12°. The reaction mixture was then stirred for a further 3 hr. at 25°, and allowed to stand overnight at 0°. The white crystals were separated by filtration, washed with water until neutral and then with aqueous ethanol. There was obtained 2.95 g. (68.9%) of crude V, m.p. 77°, which after one crystallization from ethanol melted at 88°.

Anal. Calcd. for $C_{13}H_{10}OS$: C, 72.86; H, 4.70. Found: C, 72.66; H, 4.90.

2,6-Dithenylidenecyclohexanone (VI). To a solution of 1.12 g. (0.01 mole) of 3-thiophenecarboxaldehyde in 7 ml. of ethanol, 0.98 g. (0.01 mole) of freshly distilled cyclohexanone, followed by 5–6 drops of 10% aqueous sodium hydroxide were slowly added, with stirring. After heating for 15 min. on the water bath, the mixture was cooled to 0°, and the yellow needles which soon separated were filtered off. The yield of crude 2,6-dithenylidenecyclohexanone (VI), m.p. 130°, was 1.0 g. (69.9%). Recrystallized twice from ethanol the pure compound melted at 139°.

Anal. Calcd. for $C_{16}H_{14}OS_2$: C, 67.09; H, 4.93. Found: C, 66.82; H, 5.10.

α-Phenyl-β-(3-thienyl)acrylonitrile (VII). This compound was prepared according to the procedure of Castle and Seese.[11] From 2.24 g. (0.02 mole) of 3-thiophenecarboxaldehyde there was obtained 2.27 g. (53.8%) of colorless VII, m.p. 65–66°. Two crystallizations from methanol raised the m.p. to 68°.

Anal. Calcd. for $C_{13}H_9NS$: C, 73.89; H, 4.29; N, 6.63. Found: C, 73.83; H, 4.39; N, 6.81.

3-(3-Thienyl)acrylic acid (VIII). A mixture of 3.36 g. (0.03 mole) of 3-thiophenecarboxaldehyde, 6.24 g. (0.06 mole) of malonic acid, 15 ml. of dry pyridine (distilled over potassium hydroxide), and 0.5 ml. of piperidine was heated on a water bath for 2 hr. and then heated to boiling for 5–10 min. After cooling, the resulting solution was poured, with stirring, into 75 ml. of water and treated with excess 25% hydrochloric acid. Filtration of the white flaky precipitate yielded 3.94 g. (85.2%) of 3-(3-thienyl)acrylic acid (VIII), m.p. 146°, which after recrystallization from 45% ethanol (twice) had m.p. 151°.

Anal. Calcd. for $C_7H_6O_2S$: C, 54.53; H, 3.92. Found: C, 54.72; H, 4.04.

3-(3-Thienyl)propionic acid (IX). 3-(3-Thienyl)acrylic acid (VIII) (1.54 g., 0.01 mole) was neutralized with 2% aqueous sodium hydroxide, diluted with 10 ml. of water, and reduced in the usual manner with 2% sodium-amalgam (at 15°). After recrystallization from water there was obtained 1.3 g. (83.3%) of white needles of the acid IX, m.p. 62–62.5° (reported[5] m.p. 61–62°).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.82; H, 5.16. Found: C, 53.80; H, 5.00.

3-Thenylmalonic acid (X). This acid was obtained according to the procedure described by Owen and Nord[7] for the preparation of 2-thenylmalonic acid. After removing the ether the solidified residue was recrystallized from benzene, affording 4.3 g. (71.5%) of 3-thenylmalonic acid (X), in the form of white needles, m.p. 140° (reported[5] m.p. 139–140°).

Anal. Calcd. for $C_8H_8O_4S$: C, 47.99; H, 4.03. Found: C, 48.06; H, 4.06.

By heating X and recrystallizing the resulting product from water, 75% of 3-(3-thienyl)propionic acid (IX), m.p. 62°, was obtained.[5]

Diethyl 3-thenylmalonate. The esterification was carried out by gently refluxing for 4 hr. a mixture of 4.0 g. (0.02 mole) of 3-thenylmalonic acid, 35 ml. of anhydrous ethanol, and 1 ml. of concentrated sulfuric acid. After removing the excess ethanol *in vacuo*, the residue was treated with 30 ml. of water, and the resulting solution extracted with ether (twice with 25 ml. portions). The usual procedure yielded 4.3 g. (83.7%) of diethyl 3-thenylmalonate, b.p. 146–150° (6 mm.), n_D^{20} 1.4950, d_4^{20} 1.1428 (reported[5,8] b.p. 146°/3 mm., 141–147°/4 mm., n_D^{20} 1.4960, d_4^{20} 1.142).

Anal. Calcd. for $C_{12}H_{16}O_4S$: C, 56.22; H, 6.29. Found: C, 56.15; H, 6.39.

3-Thiophenecarboxaldehyde thiosemicarbazone. To 0.56 g. (0.005 mole) of 3-thiophenecarboxaldehyde dissolved in 6 ml. of ethanol and containing 0.5 ml. of glacial acetic acid was added a warm solution of 0.46 g. (0.005 mole) of thiosemicarbazide in 9 ml. of water, with constant stirring. A white crystalline precipitate was immediately formed.

(7) Campaigne and Patrick, *J. Am. Chem. Soc.*, **77**, 5425 (1955).

(8) Campaigne, Monroe, Arnwine, and Archer, *J. Am. Chem. Soc.*, **75**, 988 (1953).

(9) All melting points are uncorrected.

(10) The microanalyses were performed by Mrs. R. Tasovac, Microanalytical Laboratory, Institute of Chemistry, Faculty of Sciences, Belgrade.

(11) Castle and Seese, *J. Org. Chem.*, **20**, 987 (1955).

Stirring was continued at room temperature for another 2 hr. Upon standing for several hours at 0°, the solid was collected by filtration and washed with ice cold 50% ethanol. There was obtained 0.77 g. (82.8%) of thiosemicarbazone, m.p. 159°. Recrystallized from 25% ethanol it melted at 160° (reported[8] m.p. 151–152°).

Anal. Calcd. for $C_6H_7N_3S_2$: C, 38.89; H, 3.80; N, 22.68. Found: C, 38.69; H, 3.88; N, 22.55.

The freshly prepared compound was white, but on standing turned yellow.

BELGRADE, YUGOSLAVIA

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF DEPAUL UNIVERSITY AND PURDUE UNIVERSITY]

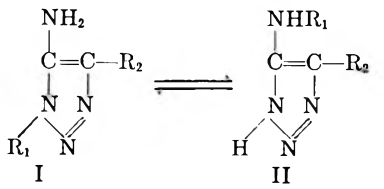
Synthesis and Isomerization of Substituted 5-Amino-1,2,3-triazoles[1]

EUGENE LIEBER,[2] TAI SIANG CHAO,[3] AND C. N. RAMACHANDRA RAO[4]

Received October 23, 1956

A series of 1,4-disubstituted-5-amino-1,2,3-triazoles were prepared by reactions involving the base-catalyzed condensation of alkyl- and aryl-azides with malonic ester, cyanoacetic ester and phenylacetonitrile. The latter proved advantageous for preparing a series of 1-substituted-4-phenyl-5-amino-1,2,3-triazoles. A mechanism is proposed for the base-catalyzed condensation of azides with phenylacetonitrile which accounts for the resistance of the electropositively substituted azides to form vicinal triazoles. The 1,4-disubstituted-5-amino-1,2,3-triazoles were irreversibly isomerized to a series of 4-phenyl-5-(substituted)anilino-1,2,3-triazoles by refluxing in pyridine-type bases. The comparative rate of irreversible isomerization of a selected group of 1-substituted-4-phenyl-5-amino-1,2,3-triazoles to 4-phenyl-5-(substituted)anilino-1,2,3-triazoles in boiling pyridine was found to depend on the electrical effect of the substituent in the 1-position in a manner comparable to that found for 1-substituted-5-aminotetrazoles. The isomerization of 1-substituted-4-phenyl-5-amino-1,2,3-triazoles to 4-phenyl-5-(substituted)anilino-1,2,3-triazoles, or *vice versa*, at 184–185° in homogeneous melts has been investigated and found to reach an equilibrium. The position of equilibrium shifts to the acidic isomer as the electronegativity of the substituent is increased, yielding an approximately linear relationship between the logarithm of the equilibrium constant and Hammett's σ-value for groups.

The discovery that 1-substituted-5-amino-1,2,3-triazoles undergo a rather facile and apparently reversible isomerization to 5-substituted amino-1,2,3-triazoles:



I II

was made by Dimroth.[5] The examples reported[5] were:

$R_1 = C_6H_5$; $R_2 = CO_2Et$ (1)

$R_1 = C_6H_5$; $R_2 = H$ (2)

$R_1 = C_6H_5$; $R_2 = C_6H_5$ (3)

$R_1 = C_6H_5$; $R_2 = CH_3$ (4)

All except example (1) were carried out under non-equilibrium conditions, *i.e.*, by use of a basic solvent which favors the acidic isomer II, or by allowing the higher melting isomer (usually II) to crystallize out from the melt. Example (1) was run in absolute ethanol and in benzene, in sealed tubes at 150° for 3 hrs. (unfortunately the tubes were cooled under ambient conditions) approaching equilibrium from either pure III or IV:

III ($R_1 = C_6H_5$; $R_2 = CO_2Et$) $\rightleftharpoons$ IV ($R_1 = C_6H_5$; $R_2 = CO_2Et$)

Dimroth's titration data[25] enable an estimation of the positions of equilibrium to be calculated. The results of these calculations are summarized in Table I. It thus appears that the reversible nature of I $\rightleftharpoons$ II has been established, although from limited data, and that the shift in the position of equilibrium with the type of solvent is in the same order as predicted by Henry, Finnegan, and Lieber[6] for substituted 5-aminotetrazoles. However, the magnitude in the shift of the position of equilibrium in a Lewis type of basic solvent appears (Table I) to be abnormally large considering the very weak basic properties of ethanol. The data for the homogeneous melt, while showing perfect coincidence regardless of the direction from which the reaction is initiated, need verification due to the questionable analytical technique[7,25] employed. Further, the limited amount

(1) Presented in part at the 128th National Meeting of the AMERICAN CHEMICAL SOCIETY, Minneapolis, Minn., September 1955.

(2) DePaul University, Chicago 14, Ill., to whom all requests for reprints and additional information should be addressed.

(3) Present address: Archer Daniel Midland Corp., Minneapolis, Minn.

(4) Department of Chemistry, Purdue University.

(5) O. Dimroth, *Ann.*, **364**, 183 (1909).

(6) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 88 (1954).

(7) A study of the determination of the weak bases and acids represented by I and II by titration in nonaqueous media has been submitted for publication elsewhere. (*Anal. Chem.*, in press.) Briefly, the determination of the acidic isomer was generally used for estimation of purity and for the determination of the positions of equilibrium. Anhydrous dimethyl formamide was used as solvent, with sodium methoxide as titrant and azoviolet as the visual indicator. The method was tested with the pure isomers of type I giving an average deviation from 100% recovery of ±0.03%.

of data and the lack of kinetic information make any postulations of mechanism untenable. The objective of this investigation was a more exhaustive examination of I $\rightleftharpoons$ II to determine whether it is a truly reversible reaction and, if so, to determine the influence of the substituents R_1 and R_2 on the position of equilibrium, the kinetics, and energetics. The present paper is concerned with the synthesis of the necessary I and II type compounds and their thermal isomerization in homogeneous melts. The present investigation differs from that recently reported by Brown, Hammick, and Heritage[25] who studied an apparent acid catalysis for the isomerization in dry ethanol for I(R_1 = *para*-substituted phenyl; R_2 = CO_2Et). A critique of this latter work will be presented in connection with our kinetic and energetics investigation of I $\rightleftharpoons$ II (R_1 = substituted phenyl; R_2 = C_6H_5) to be reported elsewhere.[8]

TABLE I

EQUILIBRIUM DATA[a] BY DIMROTH[b]

Starting Triazole	Solvent	% 5-Substituted Aminotriazole at Equilibrium[c]
1-Phenyl-4-carbethoxy-5-amino	Ethanol[d]	76.3
5-Anilino-4-carbethoxy	Ethanol[d]	76.2
1-Phenyl-4-carbethoxy-5-amino	Benzene[d]	56.3
5-Anilino-4-carbethoxy	Benzene[d]	58.2
5-Anilino-4-carbethoxy	Ether[d]	92.7
1,4-Diphenyl-5-amino	None[e]	75
4-Phenyl-5-anilino	None[e]	75

[a] Calculated from titration data. [b] Reference 5. [c] Form II. [d] In sealed tubes at 150° for 3 hours. [e] In homogeneous melt probably above 180° but not stated.

SYNTHESIS OF 1,4-SUBSTITUTED-5-AMINO-1,2,3-TRIAZOLES

From an examination of the literature[5,9-11] three routes were tested for the synthesis of type I compounds summarized in Fig. 1. The most convenient route leading directly to the desired compounds of type I was found to be sequence (C) (Fig. 1, VIII, R_1 = C_6H_5, and substituted aryl; R_2 = C_6H_5). Thus, the initial experiments with phenyl azide and phenylacetonitrile led to practically quantitative yields of pure 1,4-diphenyl-1,2,3-triazole:

$$C_6H_5N_3 + C_6H_5CH_2CN \xrightarrow{OMe^-} I\ (R_1 = R_2 = C_6H_5)$$

The method was first described by Dimroth.[10] The organic azides required for all syntheses are listed in Table II. Table III summarizes the 1-substituted-4-phenyl-5-amino-1,2,3-triazoles prepared by the condensation of phenylacetonitrile with the respective azides. The new compounds are so indicated in Table III.

FIG. 1. SYNTHESIS OF SUBSTITUTED 5-AMINO-1,2,3-TRIAZOLES

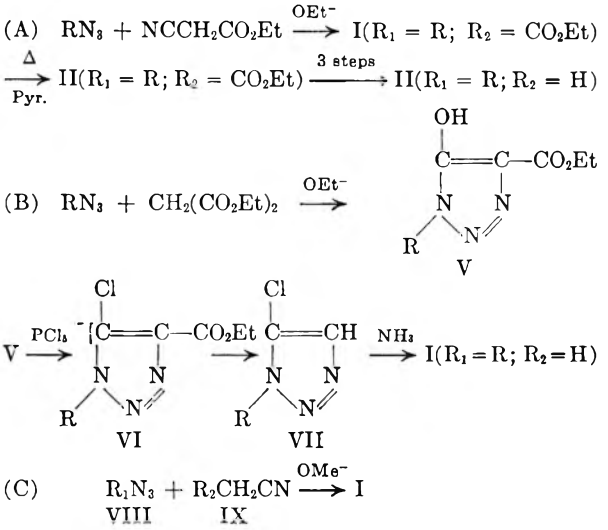


TABLE II

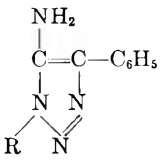
ORGANIC AZIDES, RN_3

R	% Yield	B.P./Mm.	n_D^{20}	M.P.	Reference
C_2H_5	92	50–50.5/745	1.3997	—	[a]
n-C_6H_{13}	87	85/63	1.4318	—	[b]
$C_6H_5CH_2$	87	78–78.5/12	1.5373	—	[c]
C_6H_5	80[d]	41–42/5	1.5598	—	[e]
4-$CH_3C_6H_4$	80[d]	55–56/4.5	1.5521	—	[f]
3-$CH_3C_6H_4$	88[d]	57.8/5	1.5527	—	[f]
2-$CH_3C_6H_4$	86[d]	61–62/7	1.5568	—	[f]
4-ClC_6H_4	60[d]	65–66/3	—	—	[f]
3-ClC_6H_4[g]	75	49–50/1.2	1.5806	—	[f]
2-ClC_6H_4[g]	67	45/0.85	1.5878	—	[f]
4-BrC_6H_4	73	69/2.1	1.6127	20	[f]
4-$NO_2C_6H_4$	77	—	—	74	[h]
3-$NO_2C_6H_4$	83	—	—	54–55	[h]
2-$NO_2C_6H_4$[i]	80	—	—	51–52	[h]
1-$C_{10}H_8$	34	—	—	12	[j]
2-$C_{10}H_8$	58	—	—	32–33	[j]
4-$CH_3OC_6H_4$	36	—	—	34–35	[k]

[a] E., Oliveri-Mandala, and G. Caronna, *Gazz. chim. ital.*, **71**, 182 (1941). [b] K. Henkel, and F. Weygand, *Ber.*, **76**. 817 (1943). [c] F. Moulin, *Helv. Chim. Acta*, **35**, 167 (1952). [d] Improved yields. [e] R. O. Lindsay, and C. F. H. Allen, *Org. Synthesis*, **22**, 96 (1942). [f] P. V. Dutt, H. R. Whitehead, and A. Wormall, *J. Chem. Soc.*, **119**, 2088 (1921), [g] B.p. and n_D^{20} are in disagreement with H. D. Spauschus, and J. M. Scott, *J. Am. Chem. Soc.*, **73**, 208 (1951). *Anal.* Calcd. for $C_6H_4ClN_3$: C, 46.92; H, 2.62; Cl, 23.09; N, 27.39. Found: for 2-$ClC_6H_4N_3$: C, 47.03; H, 2.61; Cl, 23.00; N, 27.43; for 3-$ClC_6H_4N_3$: C, 46.97; H, 2.69; Cl, 23.01; N, 27.47. [h] E., Noelting, E. Grandmongin, and O. Michel, *Ber.*, **25**, 3338 (1892) by the reaction of N_2H_4 with the diazonium sulfate. [i] New method of preparation. *Anal.* Calcd. for $C_6H_4BrN_3$: C, 36.40; H, 2.02; Br, 40.36. Found: C, 36.33; H, 2.27; Br, 40.5.. [j] M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **91**, 1942 (1907). [k] The compound reported as *p*-anisyl azide by F. Moulin, *Helv. Chim. Acta*, **35**, 167 (1952) is actually *p*-methoxybenzyl azide.

(8) E. Lieber, C. N. R. Rao, and T. S. Chao, *J. Am. Chem. Soc.*, in press.
(9) O. Dimroth and W. Michaelis, *Ann.*, **459**, 44 (1927).
(10) Dimroth, *Ber.*, **35**, 1034 (1902).
(11) F. R. Benson and W. L. Savill, *Chem. Revs.*, **46**, 1 (1950).

TABLE III

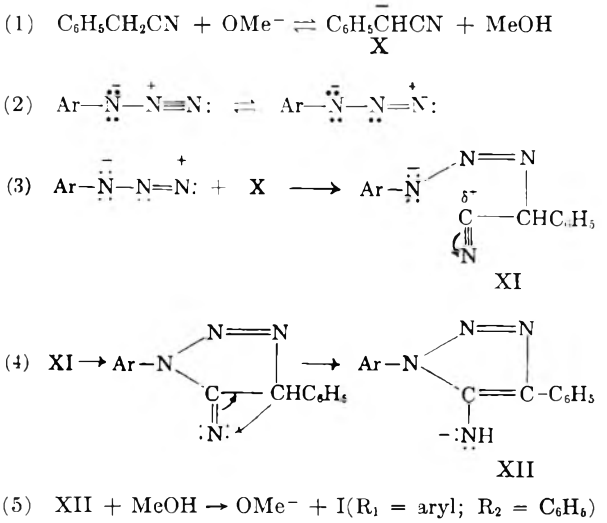


1-Substituted-4-Phenyl-5-Amino-1,2,3-Triazoles

R =	Moles of Azide Used[a]	Procedure[b]	Crystallized from	M.P.	% Yield[c]	Analysis: Calcd. % C	% H	% N	Analysis: Found % C	% H	% N
C_6H_5[d]	0.3	A	Ethanol[e]	169–170	99	71.16	5.12	23.72	71.24	4.92	23.65
4-$CH_3C_6H_4$	0.1	B	Methanol	175–176	92	71.97	5.64	22.39	71.78	5.85	22.32
3-$CH_3C_6H_4$	0.1	B	Ethyl Acetate	143–144	90	71.97	5.64	22.39	72.08	5.97	22.55
2-$CH_3C_6H_4$	0.11	C	Benzene	116–117	59	71.97	5.64	22.39	71.77	5.80	22.46
4-ClC_6H_4	0.052	A	Benzene	187–188	99	62.11	4.10	20.70	61.90	4.38	20.79
3-ClC_6H_4	0.052	A	Methanol	152	99	62.11	4.10	20.70	61.90	4.38	20.90
2-ClC_6H_4	0.05	C	Toluene	116–117	95	62.11	4.10	20.70	62.05	4.19	20.58
4-$NO_2C_6H_4$[f]	0.28	C, D	Ethyl Acetate	182–183	82	59.78	3.94	24.90	59.83	3.90	25.01
3-$NO_2C_6H_4$[g]	0.1	A	Ethyl Acetate	171–172	51	59.78	3.94	24.90	59.76	4.04	25.20
4-$CH_3OC_6H_4$	0.134	F	Ethyl Acetate	163–164	82	67.65	5.30	21.04	67.52	5.25	21.08
4-BrC_6H_4[h]	0.05	B	Benzene	188–189	71	53.36	3.33	17.78	53.50	3.68	17.83
2-$C_{10}H_7$	0.12	E	Ethyl Acetate	184–185	89	75.50	4.93	19.57	75.73	5.11	19.60
$C_6H_5CH_2$	0.2	G	Benzene[i]	157–158	59[j]	72.31	5.21	22.48	72.19	5.50	22.55

[a] Approximately a 10% excess of phenylacetonitrile and sodium methoxide (dissolved in dry ethanol or methanol) were used. [b] The general procedures are: A. Methoxide was added dropwise to a mixture of azide and nitrile cooled in an ice bath. The mixture was maintained at ice bath temperature overnight and warmed to room temperature (5 hr. to overnight) until precipitation appeared complete. B. If precipitation of the product did not occur, the above procedure was modified by allowing the reactants to warm up to ≤5–65° for periods until precipitation appeared to be complete. C. Described in Experimental Section. D. Same procedure as A, except that the precipitate obtained was recovered, and the mother liquor refluxed for an additional period. E. The azide, in dry ether, was added last; otherwise the same as A. F. Same procedure as E except that reaction mixture was refluxed at 45–55° for 10 hr., allowing the ether to escape through the hot condenser. G. Same procedure as E except that the reaction mixture was refluxed at 60–65° for 90 hr. [c] Includes work-up of all mother liquors. [d] O. Dimroth[21]; E. Lieber, T. S. Chao and C. N. R. Rao, *Org. Syntheses*, in press. [e] Precipitate washed on the funnel. [f] Dimroth's[9] procedure gave a yield of 54%. [g] The procedure of Dimroth[9] described for R = 4-$NO_2C_6H_4$ gave a yield of 24%. [h] Calcd.: Br, 25.36; Found, 25.20. [i] Product first washed on funnel with dry methanol and ether, respectively, before recrystallizing. [j] Time of reflux has an important bearing on yield, a replicate run for 60 hr. gave a yield of 36%.

Fig. 2. Mechanism for Condensation of Aryl Azides with Phenylacetonitrile



The mechanism outlined in Fig. 2 is proposed for the condensation reaction between an organic azide with phenylacetonitrile in the presence of a base. Step (1) explains the role of the sodium methoxide and why quantities in slight excess of the stoichiometric in methoxide ion are needed. An experiment using small amounts of triethylamine failed to cause condensation of phenyl azide and phenylacetonitrile. Step (2) indicates why an electron-withdrawing group enhances reaction and an electron-releasing group renders the reaction difficult. Without the help of an electron-withdrawing group at Ar, it would be difficult for the electron-pair to move from the triple bond to the middle nitrogen of the azido-group. The net result of this shift is to move a positive charge farther away from a negative charge. The (3) to (5) steps, inclusive, should be fast since they involve the neutralization of a positive and negative charge. The ring closure step (4) should not be influenced to any great extent by the nature of Ar since the electron shifting occurs away from it. Accordingly, the process is controlled by step (2) which is in turn controlled by the nature of the Ar group. This is in agreement with the experimental results which showed that the formation of I (R_1 = aryl; R_2 = C_6H_5) is favored by negatively substituted aromatic groups in the azide molecule. Thus, while the condensation of nitro-, chloro-, and bromophenyl azides, respectively, with phenylacetonitrile proceeds readily at room temperature, several hours heating was required in the

case of tolyl, naphthyl, and anisyl azides, and prolonged heating (70–92 hrs.) was required for benzyl, ethyl, and *n*-hexyl azides. The yields of I (R_1 = aryl; R_2 = C_6H_5) were very high for most aromatic azides, somewhat lower for *p*-anisyl and benzyl azides, and were very low for alkyl azides (Table III).

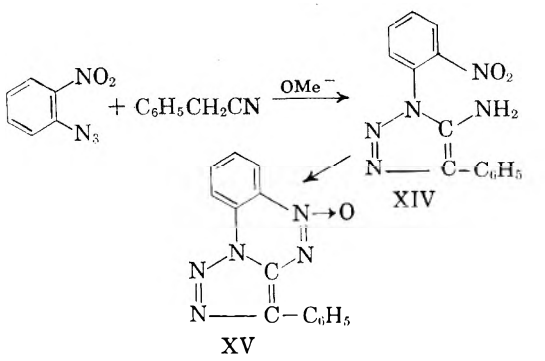
A study was made as to the effect of reaction conditions on the yield and purity of I (R_1 = nitrophenyl; R_2 = C_6H_5) resulting from the condensation of the respective isomeric nitrophenyl azides with phenylacetonitrile. The results indicated that considerable increase in yield was obtained if the reactants were allowed to stir overnight at room temperature before refluxing. Indeed, marked improvement in yield was observed by mixing the nitrophenyl azide and phenylacetonitrile at ice bath temperature and adding the sodium methoxide dropwise. The products so obtained, with the exception of *o*-nitrophenyl azide, discussed below, contained less of the acidic isomer II (R_1 = nitrophenyl; R_2 = C_6H_5) and showed a melting point 6–7° higher than products obtained at higher initial reaction temperatures. The manner in which the three reactants were brought together had only a minor effect on the yield. The importance of controlling the initial condensation temperature for the nitro-aryl azides is illustrated by the increase in yield of 1-*m*-nitrophenyl-4-phenyl-5-amino-1,2,3-triazole from 24 to 51%. The decrease in yield at higher initial condensation temperatures may be due to the instability of the nitrophenyl azides, the instability of the triazoles, or the occurrence of side reactions.

Within a given series of isomeric phenyl azides the ease of condensation with phenylacetonitrile was in the order *para* > *meta* > *ortho*. Considerable difficulties were encountered with *ortho* substituted aryl azides both in the condensation and isolation of product, due to the greater solubility of the latter in methanol and benzene. Intractable oils were usually obtained which were induced to crystallize only after considerable trial and error. It was necessary to determine the optimum reflux time for the *ortho* substituted phenyl azides in order to obtain maximum yield of the triazoles.

One important problem in connection with the preparation of I and II is the isolation of a pure isomer instead of a mixture of the two isomeric forms. Based upon the experience with the aminotetrazoles[12] it was believed that the isomerization would not proceed to such an extent as to prevent their recrystallization from solvents of reasonably low boiling points. However, a lowering of melting point and appearance of the acidic isomer was observed on recrystallization from boiling solvents. For example, 1-*p*-chlorophenyl-4-phenyl-5-amino-1,2,3-triazole had a melting point of 187–188° when recrystallized once from benzene. Upon further recrystallization from boiling dry ethanol, the product had a melting point of 185–186° which was found to be due to a 4 per cent conversion into 4-phenyl-5-(*p*-chlorophenyl)amino-1,2,3-triazole. Preliminary experiments indicated that this isomerization is more pronounced in polar than in nonpolar solvents. An experiment was thus designed to determine the effect of the nature of the solvent on the extent of isomerization during recrystallization. 1-*p*-Nitrophenyl-4-phenyl-5-amino-1,2,3-triazole, XIII (R_1 = 4-NO_2-C_6H_4; R_2 = C_6H_5), a compound which shows the highest rate of isomerization (discussed below) was selected for this purpose. A definite amount of XIII, which had been repeatedly washed with methanol but never recrystallized, was stirred individually with a number of solvents at their respective boiling points (except dimethyl formamide which was kept at 82–85°) for a definite period of time. After cooling, the crystals were filtered, washed, dried, and analyzed[7] for content of acidic isomer. The solvents used were benzene, absolute ethanol, ethyl acetate, 60% aqueous dimethyl formamide, and acetone, in order of increasing dielectric constant. It was found that the percentage of acidic isomer in the recrystallized product increases in the same order, while the melting point of the product decreases accordingly (Table VIII). This means that the isomerization into the acidic isomer is enhanced by the use of the more polar solvent. For purpose of purification of the basic isomer (I), benzene is the recommended solvent. If the solubility in this solvent is too low, the use of ethanol or ethyl acetate may be the second best choice. In all cases, however, the heating period must be kept as short as possible and the temperature as low as possible. It was found to be good practice to heat up the solvent first before adding the compound to be recrystallized. This is particularly important in the cases of I where the 1-substituent is a strong electronegative group. Washing with ether was found to be an advantageous means of removing small amounts of II from I due to the fact that the basic isomers are almost insoluble in this solvent, while that of the acidic isomer may be very high. Crude XIII, having a melting point of 171–176° and containing about 4% of the corresponding acidic isomer, on washing with ether gave a product melting at 181–182° and containing only 0.36% of acidic isomer. However, as pointed out previously, low temperature control of the initial condensation is a much more important factor leading to a pure type I where R_1 is a strong electronegative group.

An orange colored product, melting at 219°, was obtained from the condensation of *o*-nitrophenyl azide and phenylacetonitrile. The analysis did not correspond to that calculated for 1-*o*-nitrophenyl-4-phenyl-5-amino-1,2,3-triazole but indicated the loss of a molecule of water. This suggests that the following reaction may have taken place:

(12) W. S. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).



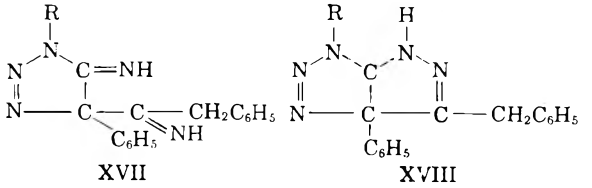
XIV XV

A second less likely possibility is the elimination of water after the isomerization of XIV to II (R_1 = 4-NO_2-C_6H_4; R_2 = C_6H_5). In either event, confirmation for the presence of the *N*-oxide group was obtained by infrared absorption spectroscopy. Further studies on the nature of the condensation product of *o*-nitrophenyl azide and phenylacetonitrile are in progress and will be reported separately.

Considerable difficulty was encountered in the condensation of ethyl- and *n*-hexyl azides with phenylacetonitrile. Two types of products were isolated, XVI (I, R_1 = C_2H_5; R_2 = C_6H_5, m.p. 111–112°) corresponding to the expected triazole and unknown products, XVII (or XVIII) whose analyses corresponds to the reactions:

$$C_2H_5N_3 + 2C_6H_5CH_2CN \xrightarrow{OMe^-} C_{18}H_{19}N_5$$

$$C_6H_{13}N_3 + 2C_6H_5CH_2CN \xrightarrow{OMe^-} C_{22}H_{27}N_5$$



XVII XVIII

This could result from an initial dimerization[14,15] followed by addition of the alkyl azide:

$$2C_6H_5CH_2CN \xrightarrow{OMe^-} \underset{\text{XIX}}{C_6H_5CH_2C(:NH)CH(C_6H_5)CN} \xrightarrow{RN_3} \underset{\text{XVII or XVIII}}{}$$

It will be noted that XVII and XVIII are isomeric. It is not surprising that an initial dimerization will take place in the presence of the less reactive alkyl azides. In the presence of the more reactive aromatic azides, this dimerization is repressed in favor of the formation of I. XVIII is derived from the ring system pyrazolo-(3,4)-v-triazole (number 584 in the Ring Index[13]) and its possible formation from preformed dimer of phenylacetonitrile, 1-cyano-2-imino-1,3-diphenylpropane, XIX, is under study and will be reported separately.

In addition to the series of 1-substituted-4-phenyl 5-amino-1,2,3-triazoles prepared (Table III), the following were synthesized in order to determine the effect of substituents in the 4-position of I and II, while maintaining R_1 constant as phenyl:

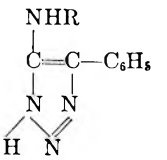
XX:I (R_1 = C_6H_5; R_2 = CO_2Et)
XXI:II (R_1 = C_6H_5; R_2 = CO_2Et)
XXII:II (R_1 = C_6H_5; R_2 = H)
XXIII:I (R_1 = C_6H_5; R_2 = H)

XX [scheme (A), Figure No. 1, R = C_6H_5] has been described by Dimroth.[5] XXI was prepared by irreversible isomerization of XX following the procedure of Dimroth and Pfister.[22] XXII was derived from XXI by saponification, acidification and decarboxylation. The preparation of XXIII involved the three step synthesis of VII (R = C_6H_5) followed by ammonolysis [Figure 1, sequence (B)].

SYNTHESIS OF 4-PHENYL-5-(SUBSTITUTED)AMINO-1,2,3-TRIAZOLES

The required pure isomers of type II were prepared from the purified compounds of type I (Table III) by an irreversible thermal isomerization in the presence of excess base. The compounds so prepared are summarized in Table IV. Pyridine was invariably used except for R = *p*-anisyl and benzyl which were isomerized in boiling 4-picoline. Longer

TABLE IV



4-PHENYL-5-SUBSTITUTED AMINO-1,2,3-TRIAZOLES

R	% Yield[b]	M.P., °C.	Analysis[a] % N calcd.	% N found
C_6H_5[c]	92[d]	167–168	23.72	23.64
4-$CH_3C_6H_4$	100[e]	158–159	22.39	22.45
3-$CH_3C_6H_4$	90[e]	168–169	22.39	22.16
2-$CH_3C_6H_4$[f]	98[g]	98–99	22.39	22.40
4-ClC_6H_4	80[d]	158–159	20.70	20.90
3-ClC_6H_4	96[e]	166–167	20.70	20.77
2-ClC_6H_4	93[g]	134–135	20.70	20.67
4-$NO_2C_6H_4$[c]	83[h]	164–165	24.90	24.85
3-$NO_2C_6H_4$[f]	100[i]	136–137	24.90	24.86
4-$CH_3OC_6H_4$[j]	100[g]	134–135	21.04	21.03
4-BrC_6H_4	90[k]	174–175	17.78	17.58
2-$C_{10}H_7$	89[d]	214–215	19.57	19.57
$C_6H_5CH_2$[l]	—	121–122	22.39	22.28

[a] In addition to the N analysis, freedom from basic isomer was determined by non-aqueous titration. [b] Recrystallized from. [c] Known compounds. [d] Ethanol-water. [e] Benzene. [f] Forms an oil which crystallizes after long standing. [g] Toluene. [h] Ether. [i] Ether-hexane. [j] 4-Picoline used as solvent at 141–142°; crystals washed with CCl_4 to remove brownish contamination. [k] Ethanol. [l] In small quantities by ether extraction of mixed isomers.

(13) A. M. Patterson and L. T. Capel, *The Ring Index*, Reinhold Publishing Corp., N. Y., 1940.

(14) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, 89, 1930 (1906).

(15) N. Lee and J. F. Thorpe, *J. Chem. Soc.*, 91, 1287 (1907).

refluxing times and completely dry solvent were needed where R was a positively substituted phenyl group. Considerable difficulty was encountered in the isomerization of 1-benzyl-4-phenyl-5-amino-1,2,3-triazole (I, $R_1 = C_6H_5CH_2$; $R_2 = C_6H_5$) into 4-phenyl-5-benzylamino-1,2,3-triazole. Even after 48 hr. refluxing in 4-picoline, the product was found to contain only 24% of the acidic isomer. Its eventual preparation in pure form was achieved by ether extraction of the mixture of isomers.

The same pronounced effect of substituents was noticed in the base-catalyzed irreversible isomerization of I to II. While there was no trouble in obtaining pure acidic isomers in the case of most negatively substituted phenyl compounds of type I, considerable difficulties were encountered for the positively substituted phenyl derivatives. The case of I ($R_1 = C_6H_5CH_2$) was particularly resistant to isomerization in boiling dry pyridine, 8 hr. refluxing producing no change in melting point. A study was made of the comparative rates of irreversible isomerization in an excess of boiling dry pyridine. The data obtained are summarized in Table V which shows that negative groups enhance the rate of isomerization in agreement with similar observations in the 5-aminotetrazole system.[6,12,16]

TABLE V

$$I\ (R_1 = R;\ R_2 = C_6H_5) \xrightarrow[\Delta]{Pyr} II\ (R_1 = R;\ R_2 = C_6H_5)$$

EFFECT OF 1-SUBSTITUTION ON THE RATE OF IRREVERSIBLE ISOMERIZATION

R	Rate ($C_6H_5CH_2 = 100$)[a,b]
$C_6H_5CH_2$	100
$4\text{-}CH_3OC_6H_4$	300
C_6H_5	700
$4\text{-}NO_2C_6H_4$	1000

[a] Based on 30-min. reaction time in boiling pyridine. [b] A similar series based on 90-min. reaction time showed the same relative order.

ISOMERIZATIONS IN HOMOGENEOUS MELTS

In order to determine whether the reaction I $\rightleftharpoons$ II represents a true equilibrium reaction, a careful study of the isomerization of pairs of isomers represented by pure I or II in homogeneous systems (undisturbed melts) was carried out at 184–185°. Preliminary experiments with $R_1 = R_2 = C_6H_5$ showed that a reaction time of 15 min. at this temperature was adequate to insure the attainment of equilibrium. The results obtained are summarized in Table VI, for all cases of I and II, respectively, in which $R_2 = C_6H_5$, while Table VII summarizes the results of maintaining $R_1 = C_6H_5$ and varying the R_2 substituent in the 4-position.

Tables VI and VII show that the equilibrium is reached starting with either of the isomeric forms I or II. The position of equilibrium is again dependent on the electrical nature of the substituent in the 1- position in a manner very nearly parallel to the effect observed in the substituted 5-aminotetrazole system[6,16] (Table VI for II, $R_2 = C_6H_5$) and in all probability a similar mechanism[16] is operative.[26] Corroboration for this appears in the plot, Fig. 3, of the logarithm of the equilibrium constant with Hammett's σ value for groups.[17] It will be noted that an approximately linear relationship is obtained. However, complete verification for the similarity in mechanism in the isomerization of the substituted 5-aminotetrazoles and the substituted 5-amino-1,2,3-triazoles must await kinetic information. This latter study will be reported in a separate communication. It is also evident from Table VII that much more information is needed regarding the effects of substituents in the 4- position of I and II on the position of equilibrium. This problem is being currently investigated.

TABLE VI

PROOF OF EQUILIBRIUM IN HOMOGENEOUS MELTS

Starting Vicinal Triazole	5-(Substituted)-amino-triazole in Equilibrium Melt[a] (%)	K[b]
1-Benzyl-5-amino-4-phenyl-	7.6	
5-Benzylamino-4-phenyl-	7.7	0.083
1-(4-Anisyl)-5-amino-4-phenyl-	50.4	
5-(4-Anisyl)amino-4-phenyl-	50.8	1.03
1-(4-Tolyl)-5-amino-4-phenyl-	65.3	
5-(4-Tolyl)amino-4-phenyl-	65.2	1.94
1-(3-Tolyl)-5-amino-4-phenyl-	69.1	
5-(3-Tolyl)amino-4-phenyl-	69.5	2.26
1-Phenyl-5-amino-4-phenyl-	77.0	
5-Anilino-4-phenyl-	77.2	3.37
1-(4-Nitrophenyl)-5-amino-4-phenyl-	94.4	
5-(4-Nitrophenyl)amino-4-phenyl-	94.4	16.9
1-(4-Bromophenyl)-5-amino-4-phenyl-	85.9	
5-(4-Bromophenyl)amino-4-phenyl-	85.8	6.14
1-(4-Chlorophenyl)-5-amino-4-phenyl-	85.1	
5-(4-Chlorophenyl)amino-4-phenyl-	85.2	5.66
1-(3-Chlorophenyl)-5-amino-4-phenyl-	89.7	
5-(3-Chlorophenyl)amino-4-phenyl	89.3	8.50
1-(2-Naphthyl)-5-amino-4-phenyl-	81.3	
5-(2-Naphthyl)amino-4-phenyl-	81.5	4.37
1-(3-Nitrophenyl)-5-amino-4-phenyl-	93.2	
5-(3-Nitrophenyl)amino-4-phenyl-	93.2	13.7

[a] At 184–185° for 15 min. [b] Equilibrium constant calculated as the ratio of II to I.

EXPERIMENTAL[18,19]

Organic azides. The organic azides used in this research

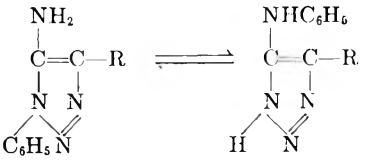
(16) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, 77, 2264 (1955).

(17) Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1940, Chapter VII.

(18) All melting points are taken on a Fisher-Johns Block and are corrected.

(19) Microanalyses by Galbraith Microanalytical Laboratories.

TABLE VII



EQUILIBRIUM MEASUREMENTS IN HOMOGENEOUS MELTS AT 184–185°. EFFECT OF 4-POSITION

R	Starting Vicinal Triazole	5-(Substituted)-aminotriazole (Acidic Form) in Equilibrium Melt (%)
C_6H_5	1-Phenyl-5-amino-	77.0
C_6H_5	5-Anilino-	77.2
H	1-Phenyl-5-amino-	67.1
H	5-Anilino-	67.2
$—CO_2Et$	1-Phenyl-5-amino-	66.4
$—CO_2Et$	5-Anilino-	67.0

and summarized in Table II were made from procedures or adaptations of procedures described in the literature. A new method for the preparation of alkyl azides, which avoids the formation of troublesome azeotropes, is described elsewhere.[20]

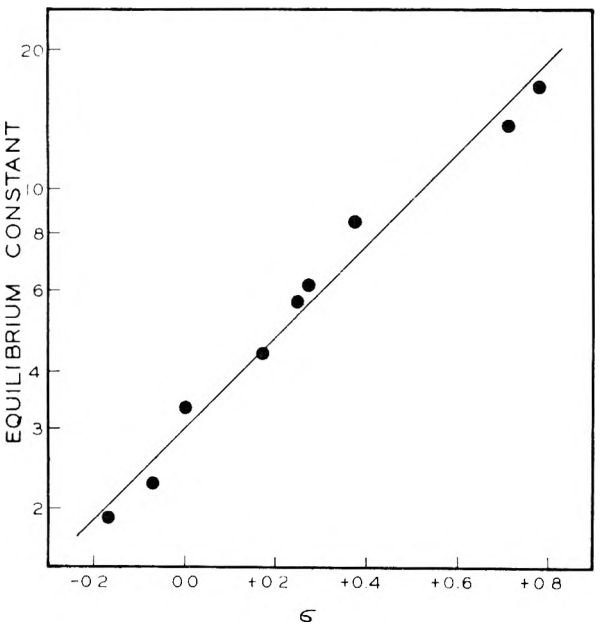


FIG. 3. CORRELATION BETWEEN EQUILIBRIUM CONSTANT AND HAMMETT'S SIGMA VALUE FOR GROUPS

1-Substituted-4-phenyl-5-amino-1,2,3-triazoles. The compounds prepared are summarized in Table III. Those preparations which differ markedly from the general procedures summarized in Table III, or gave particular difficulty in recovery of product, are given below.

1-o-Tolyl-4-phenyl-5-amino-1,2,3-triazole. While the procedure was substantially that of B (Table III), considerable difficulty was experienced in isolating a solid product. This was overcome after some modifications in the procedure. The following was the best procedure. The reaction flask was charged with 12.9 g. (0.11 mole) of phenylacetonitrile and a solution of 8.1 g. (0.15 mole) of sodium methoxide in 100 ml. of methanol. With constant stirring at room temperature, a solution of 13.3 g. (0.1 mole) of *o*-tolyl azide in 10 ml. of methanol was added dropwise over 1 hr. The reaction mixture was stirred at room temperature overnight (no precipitation was observed) and then refluxed for a total of 30 hr. at 65–75°. The reaction mixture, after cooling to room temperature, was filtered from the small amount of sodium methoxide which had precipitated, and the filtrate evaporated under vacuum until free of methanol. The residue was an intractable dark red thick oil. It was diluted with 300 ml. of benzene and filtered to remove the sodium methoxide. The filtrate was then evaporated under vacuum to remove the benzene and the oily residue containing some precipitated solid (later identified as sodium methoxide) was extracted with about 200 ml. of ether. The ether solution was evaporated at room temperature with occasional stirring. When the volume was reduced to about 100 ml. turbidity was observed, and, upon stirring, a rapid crystallization took place. After standing for 2 hr., the light brown, large crystals were filtered and suction dried. Yield, 11.5 g. with an additional 3.2 g. obtained by further concentration of the mother liquor.

1-o-Chlorophenyl-4-phenyl-5-amino-1,2,3-triazole. As in the case of *o*-tolyl azide, considerable difficulty was experienced in isolating a solid product. The inability of conveniently isolating a solid product was the occasion for a study in recovery methods. The difficulties were finally overcome and the yield markedly improved by diluting with benzene and filtering, after which the entire reaction mixture was poured slowly into ice water. A white semisolid was formed, which, after standing under water at room temperature for 8 days, turned into a yellowish-white crystalline solid. This was broken up, filtered, suction and air-dried. From 7.67 g. (0.05 mole) of *o*-chlorophenyl azide was obtained 12 g. of product.

1-p-Nitrophenyl-4-phenyl-5-amino-1,2,3-triazole (XIII). The procedure of Dimroth and Michaelis[9] yields 53.5% of this product (from 0.0277 mole of *p*-nitrophenyl azide). It was best modified by carrying out the initial condensation at 0–3° and stirring overnight, recovering the product and refluxing the filtrate for 4 hrs. for a combined yield of 11.5 g. (81.8%).

In a series of experiments in which the initial and final conditions in the condensation of *p*-nitrophenyl azide (0.05 mole) with phenylacetonitrile were varied, it was found that the purity of the product, *i.e.*, lack of acidic isomer, was favored by low temperature, although this factor very materially reduces the yield. Thus, when the reagents were reacted at room temperature and then refluxed 4 hr. the yield was 57% and the m.p. 175–176° whereas, when the reagents were reacted at 0–3° (1 hour) and then overnight at room temperature, the yield was 20.7% but the m.p. was 181–182° (the pure isomer melts at 182–183°) and the content of acidic isomer by nonaqueous titration[7] was 0.36%. Relatively impure samples of product having a m.p. of 170–175° were readily freed of acidic isomer by washing with dry ether. About 5 g. of material, m.p. 171–172°, in the form of very fine crystals, was placed on a sintered glass funnel and washed with four 50-ml. portions of ether. After suction and air-drying, the melting point was found to be 181–182°. Table VIII summarizes the effect of solvent and temperature on the extent of isomerization that occurs during recrystallization.

Condensation of o-nitrophenyl azide with phenylacetonitrile (XV). A mixture of 100 ml. of dry ether, 16.6 g. (0.10 mole) of *o*-nitrophenyl azide and 11.7 g. (0.10 mole) of phenylacetonitrile was treated dropwise, with constant stirring at 0°, with a solution of 5.4 g. (0.10 mole) of sodium methoxide (in 50 ml. of methanol) over a period of 2 hr. The mixture was stirred at 0–20° (in a melting ice bath) overnight and then at room temperature for 6 hr. The solid product was filtered from the dark colored solution and washed with 200 ml. of ether and 40 ml. of methanol. There was obtained

(20) E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, 22, 238 (1957).

TABLE VIII

EFFECT OF SOLVENT AND TEMPERATURE ON ISOMERIZATION OF 1-*p*-NITROPHENYL-4-PHENYL-5-AMINO-1,2,3-TRIAZOLE

Solvent	Conditions[a] Temp., °C.	Triazole used, g.	Solvent used, ml.	Recovered M.P.	Recovered Isomer[b]
Benzene	80	0.6	600	177–178	2.55
Abs. ethanol	78	0.8	300	175–176	2.58
Ethyl acetate	77	0.5	100	175–176	3.90
DMF[c]	82–85	1.0	20	172.5–173.5	4.45
Acetone	56	1.0	20	173–174	5.74
(Before recrystallization)				177–178	0.31

[a] The triazole was maintained at the specific temperatures for 5 min., filtered, and allowed to crystallize. [b] Per cent acidic isomer by nonaqueous titration.[7] [c] Dimethyl formamide, 60% aqueous solution.

7.8 g. of orange colored needle-like crystals, m.p. 220–222°, dec.; after four recrystallizations from ethyl acetate, m.p. 218–219° (dec.).

Anal. Calcd. for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.61. Found: C, 64.14; H, 3.66; N, 26.80.

Condensation of ethyl azide with phenylacetonitrile. 1-Ethyl-4-phenyl-5-amino-1,2,3-triazole (XVI, XVII, and XVIII). A solution of sodium ethoxide in 100 ml. of ethanol was prepared under a stream of dry nitrogen from 5.06 g. (0.22 mole) of sodium. After cooling the flask to room temperature and immersing it in an ice bath, 25.7 g. (0.22 mole) of phenylacetonitrile and 13.8 g. (0.194 mole) of ethyl azide were added. A Dry-Ice trap was connected to the top of the reflux condenser to prevent any loss of ethyl azide. The reaction mixture was allowed to warm up to room temperature and then heated slowly to 60° and maintained there for 70 hr. The reaction mixture was then cooled to −17°. The crystals which separated out were filtered and washed with 50 ml. of methanol. After suction and air-drying, 14.8 g. of small white crystals, m.p. 147–148°, was obtained. Upon evaporation of the mother liquor, a second crop of 8 g., a third one of 6.6 g., and a fourth of 1.5 g. were obtained.

The first crop of product on successive recrystallization from hot benzene gave fine white needles of constant m.p. of 151–152°. It was identified as XVII (or XVIII) by analysis (R = C_2H_5).

Anal. Calcd. for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27; N, 22.94. Found: C, 70.60; H, 6.20; N, 22.97.

The second, third and fourth crops of crystals were combined and recrystallized successively from boiling benzene to a constant m.p. of 111–112°. The compound was identified as XVI (R = C_2H_5).

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43. Found: C, 64.57; H, 6.49.

Condensation of n-hexyl azide with phenylacetonitrile (XVII or XVIII, R = C_6H_{13}). The reaction mixture comprised 14 g. (0.12 mole) of phenylacetonitrile, 8.65 g. (0.16 mole) of sodium methoxide (in 70 ml. of methanol) and 14 g. (0.11 mole) of *n*-hexyl azide (in 30 ml. of methanol) added last. The reaction was maintained at room temperature overnight and then refluxed at 62–65° for 73 hrs. Upon vacuum evaporation to about 50 ml., 2.3 g. of yellowish solid precipitated which was washed with ethanol and ether and recrystallized from toluene to white shiny crystals, m.p. 196–197°.

Anal. Calcd. for $C_{22}H_{27}N_5$: C, 73.09; H, 7.53; N, 19.38. Found: C, 72.41; H, 7.54; N, 20.31.

The mother liquor was decomposed by ice water, yielding an oily layer extractable by benzene. Removal of the benzene gave an oil from which no crystallization could be induced.

Ethyl 1-phenyl-5-amino-1,2,3-triazole-4-carboxylate (XX). This was prepared by the method of Dimroth[5] from 0.42 mole of phenyl azide and 0.44 mole of ethyl cyanoacetate. Yield, 67 g. (69%), m.p. 126°.[5]

Ethyl 5-anilino-1,2,3-triazole-4-carboxylate (XXI). This was prepared by irreversible isomerization of XX following the procedure of Dimroth and Pfister.[22] From 5 g. of XX, yield 4 g. (80%), fine feltlike needles, m.p. 129–130°.[23]

5-Anilino-1,2,3-triazole (XXII). By saponification of 6 g. of XXI with alcoholic KOH, isolation and acidification gave 4 g. (77%) of *5-anilino-1,2,3-triazole-4-carboxylic acid*. After drying it was decarboxylated at 152–154° and recrystallized from hot water. Yield, 2.8 g. (90% based on the carboxylic acid), m.p. 139°.[5]

1-Phenyl-4-chloro-1,2,3-triazole (XXVI). From 0.3 mole of methyl 1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylate[24] and PCl_5 was obtained 41 g. (57%) of *methyl 1-phenyl-5-chloro-1,2,3-triazole-4-carboxylate*, m.p. 87°[24] (XXIV). From 0.1 mole of XXIV by saponification and acidification was obtained 15.6 g. (70%) of *1-phenyl-5-chloro-1,2,3-triazole-4-carboxylic acid* (XXV), m.p. 134°. Without purification, 0.7 mole of XXV on thermal decarboxylation gave 10.8 g. (84%) of XXVI, m.p. 47–48°.

1-Phenyl-5-amino-1,2,3-triazole (XXIII). By ammonolysis of 1.8 g. (0.01 mole) of XXVI in ethanolic ammonia in a sealed tube at room temperature for five weeks. Yield, 0.5 g. (31%), m.p. 110–111°.[5]

4-Phenyl-5-substituted-amino-1,2,3-triazoles. Table IV. Except where noted the preparation of *4-phenyl-5-(p-tolyl)-amino-1,2,3-triazole* was typical.

Five g. (0.02 mole) of *1-p-tolyl-4-phenyl-5-amino-1,2,3-triazole* was dissolved in 20 ml. of dry pyridine. The solution was refluxed at 113–115° for 48 hr. After cooling, it was filtered into 500 ml. of ice water. A white semisolid was formed which, after standing 1 hr., with occasional stirring and scratching, crystallized. It was filtered, washed twice with water, and suctioned and air-dried. Yield, 5 g. Recrystallized from 100 ml. of hot benzene into fine, white needles. A nonaqueous titration showed the absence of basic isomer.[7]

4-Phenyl-5-(m-nitrophenyl)amino-1,2,3-triazole. Seven g. (0.025 mole) of *1-m-nitrophenyl-4-phenyl-5-amino-1,2,3-triazole* was mixed with 30 ml. of dry pyridine. The compound dissolved on warming the pyridine to reflux, which was maintained for 12 hr. After cooling, it was filtered into 500 ml. of ice water, whereupon a brownish colored oil separated. The latter did not crystallize after standing several hours with occasional stirring and scratching. However, after several days at room temperature, solidification was achieved. It was filtered and washed with three 40-ml. portions of water. After suction and air-drying, the yield was 7 g. The compound is very soluble in ether, benzene, and methanol and insoluble in cyclohexane. Recrystallization from aqueous methanol yielded irregular crystals, m.p. 134–136°. It is best recrystallized by dissolving in ether, diluting with 2 volumes of petroleum ether, and evaporating slowly to produce deep yellow crystals.

4-Phenyl-5-benzylamino-1,2,3-triazole. Commercial 4-picoline was dried over NaOH pellets and fractionally distilled over the same reagent. The middle fraction, b.p. 143–145° was used. Eight and one-half g. (0.034 mole) of 1-benzyl-4-phenyl-5-amino-1,2,3-triazole was dissolved in 30 ml. of purified 4-picoline, refluxed for 108 hours at 131–132° and cooled to room temperature. No crystals separated. The solution was poured into ice water and the white precipitate, after standing 3 hr., was filtered, washed with water and air-dried. Yield 6.7 g., m.p. 130–132°. Acidimetric titration in nonaqueous solvent[7] showed the presence of 23% of the desired product, indicating that the isomerization was still far from complete even under the drastic conditions used.

About 6 g. of the above mixture was placed in a sintered

(21) O. Dimroth, *Ber.*, **35**, 4058 (1902).
(22) O. Dimroth and K. Pfister, *Ber.*, **43**, 2736 (1910).
(23) O. Dimroth, *Ann.*, **364**, 203 (1909).
(24) O. Dimroth, *Ann.*, **335**, 1 (1904).

glass funnel and extracted with ten 20-ml. portions of dry ether. The ether was removed by evaporation at room temperature. Yield, 1.5 g., white crystals. Nonaqueous titration showed it to be free of the basic isomer.

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.97; H, 5.64; N, 22.39. Found: C, 71.80; H, 5.51; N, 22.28.

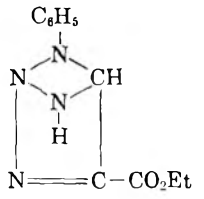
Relative rates of irreversible isomerization (I to II). *Table V.* One g. of each compound in 8 ml. of dry pyridine was refluxed 0.5 hr. on a preheated sand bath. The reaction mixture was poured into 150 ml. of ice water. The product was filtered, washed several times with water and thoroughly dried. The acidic isomer content was determined by titration in nonaqueous solvent.[7]

Equilibrium measurements in homogeneous melts, Table VI. Known quantities of I and II, respectively, were taken in sample tubes with standard inner joints which could be fitted to the two side necks of a 500 ml. 3-necked flask. A reflux condenser and a thermometer well were fitted to the central neck of the flask. Boiling *trans*-decalin gave a temperature of 184–185°. The samples were maintained at this temperature in the molten condition for a known period of time, after which they were chilled to ice temperature and then estimated for type II isomer by nonaqueous techniques.[7,25]

Acknowledgment. A grant-in-aid in support of this investigation from the Office of Naval Research is gratefully acknowledged.

(25) Dimroth, *Ann.*, **377**, 211 (1910) and Brown, Hammick, and Heritage, *J. Chem. Soc.*, 3820 (1953) used alcoholic potassium hydroxide as titrant and phenolphthalein as visible indicator. The accuracy of this work is questionable. For example, the titration of 4-phenyl-5-anilino- and 4-phenyl-5-(*m*-chlorophenyl)amino-1,2,3-triazoles, respectively, in dry ethanol as solvent, sodium methoxide in dry methanol as the titrant and phenolphthalein as visible indicator, gave consistently only 85 to 87 per cent recoveries. Furthermore, it was found necessary to standardize on the shade of the pink (or the red) of the indicator endpoint, otherwise the recovery values were found to lie anywhere between 68 to 98% recoveries (only the stronger 4-substituted-5-(substituted)amino-1,2,3-triazoles gave the higher recovery values. Details of this study are reported elsewhere.[7]

(26) Attention is directed to the polemic between Dutt [*J. Chem. Soc.*, 265 (1923); 2476 (1924)] and Dimroth[5] regarding the structure of II (R_1 = C_6H_5; R_2 = CO_2Et). Dutt considered the structure to be as indicated at end of this footnote. Attempts to answer this on chemical grounds were made by Dimroth and Michaelis.[9] However, it can be stated that the arguments on either side were not entirely convincing. Dutt's hypothesis of a bicyclic intermediate does not definitely account for the influence of R_1 in I and II on either the position of equilibrium or the relative rate of isomerization.[8] The high degree of ring strain required by this type of intermediate would make its formation very unlikely. W. L. Garbrecht, and R. M., Herbst, *J. Org. Chem.*, **18**, 1269 (1953) have suggested a similar bicyclic intermediate to account for the isomerization of substituted 5-aminotetrazoles[6,10] which is open to the same objections.



CHICAGO 14, ILL.

[CONTRIBUTION FROM ORGANIC CHEMICALS DEPARTMENT RESEARCH DIVISION, JACKSON LABORATORY, E. I. DU PONT DE NEMOURS & CO., INC.]

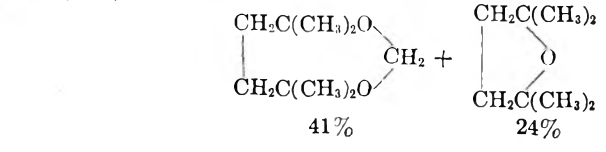
Seven-Membered Cyclic Acetals

DEXTER B. PATTISON

Received December 13, 1956

The general method for the synthesis of 1,3-dioxepane has been extended to eight novel seven-membered cyclic acetals, including 1,3-dioxep-5-ene. The method has been improved.

This paper describes the preparation and properties of various seven-membered cyclic acetals derived from aldehydes and dihydric alcohols containing four carbon atoms between hydroxyl groups. There are two competing reactions which can occur, either ring closure to the desired seven-membered acetal or dehydration of the glycol to a tetrahydrofuran derivative. This is illustrated below in the equation for the synthesis of 4,4,7,7-tetramethyl-1,3-dioxepane.



Substituents on the alpha carbon atoms and to a much lesser extent on the beta position of the diol favor the formation of the tetrahydrofuran derivative and lower the yield of the 1,3-dioxepane. On the other hand, with a double bond beta to the hydroxyl groups of the diol only a trace of dihydrofuran could be isolated.

The reaction of *cis*-2-butenediol-1,4 with formaldehyde to give 1,3-dioxep-5-ene[1] and the reaction of *cis*-2-butenediol-1,4 with various aldehydes to give substituted 1,3-dioxep-5-enes[2] has been described in recent papers. The double bond in 1,3-dioxep-5-ene appears to have normal double bond activity. 1,3-Dioxep-5-ene adds bro-

(1) W. Reppe, *et al.*, *Ann.*, 596, 1 (1956).

(2) W. Brannock and G. Lappin, *J. Org. Chem.*, 21, 1366 (1956).

mine readily in almost quantitative yield to give 5,6-dibromo-1,3-dioxepane, and addition of chlorine gives 5,6-dichloro-1,3-dioxepane.

In the literature only 1,3-dioxepane[3] and derivatives with a methyl[4,5] or furyl[6] substituent in the 2-position have been described, and yields have been mediocre. The synthesis of 4,4′,7,7′-tetramethyl-bis(1,3-dioxepane) from glyoxal and 2,5-hexanediol[7] has been described. The present work has shown that 1,3-dioxepane can be made easily in 90% yield and substituted derivatives can also be made in high yield as shown in Table I.

TABLE I

ACETALS FROM DIOLS AND ALDEHYDES

Diol	Aldehyde	% Yield of Cyclic acetal	% Yield of Furan derivative	Properties of the Cyclic Acetals B.p., °C.	Pressure mm.	n_D^{25}	Found % C	Found % H	Calcd. % C	Calcd. % H
1,4-Butanediol	Formaldehyde	90	3	119	760	1.4275	58.5	10.1	58.8	9.8
2-Methyl-1,4-butanediol	Formaldehyde	78	2	72	93	1.4269	62.0	10.4	62.1	10.4
2,5-Hexanediol	Formaldehyde	82	4	80	80	1.4230	63.4	10.7	64.6	10.8
2,5-Dimethyl-2,5-hexanediol	Formaldehyde	41	24	112	115	1.4365	68.5	11.5	68.4	11.4
2,2,3,3-Tetrafluoro-1,4-butanediol	Formaldehyde	84	1	132	760	1.3620	34.7	3.5	34.5	3.5
2-Butenediol-1,4	Formaldehyde	69	0.5	127	760	1.4540	60.0	8.3	60.0	8.0
2-Butenediol-1,4	*n*-Heptaldehyde	53	...	93	2	1.4527	71.7	11.1	71.7	10.9
2-Butenediol-1,4	Benzaldehyde	30	...	114	3.5	1.5387	74.2	6.9	75.0	6.8

All of these compounds appeared to be homogeneous and had definite boiling points except in one case. 4,7-Dimethyl-1,3-dioxepane apparently was a mixture of two isomers, which had different refractive indices and about 6–8° difference in boiling point. They are believed to be *cis* and *trans* isomers.

EXPERIMENTAL

Most of the diols used in this work are commercially available. In two cases studied purification of the diol did not improve the yield of the resultant cyclic acetal. 2-Methyl-1,4-butanediol was made by Dr. J. Burt of this laboratory by the reduction of dimethyl 2-methylsuccinate under 4500 p.s.i. hydrogen pressure using Harshaw 1402P copper chromite catalyst at 250° for 5 hr. Preparation of 2,2,3,3-tetrafluoro-1,4-butanediol[8] and 5,5,6,6-tetrafluoro-1,3-dioxepane was done by Dr. S. Dixon of this laboratory.

1,3-Dioxepane. The writer placed 3013 g. of commercial 1,4-butanediol (33.5 moles), 1100 g. paraformaldehyde (34.8 moles, assuming 95% purity), 2 g. *N*-phenyl-2-naphthylamine, 5 g. *p*-toluenesulfonic acid, and some boiling chips in a 5-liter flask fitted with a thermometer with the bulb near the bottom of the flask, a dropping funnel, and a condenser arranged for downward distillation. The mixture was heated rapidly. The distillate initially contained two layers which were separated. The upper layer was mostly 1,3-dioxepane, and the lower layer contained mostly water together with 11–13% formaldehyde and some 1,3-dioxepane. As the distillation proceeded, the amount of aqueous layer decreased and eventually 1,3-dioxepane came over with no aqueous layer.

When the volume in the distillation pot was 500–1000 ml., part of the aqueous distillate was returned dropwise to the pot so that the pot temperature was maintained at 180–200°. Distillation was continued until almost no material remained in the flask. The last 200–500 ml. of the distillate was light brown and the rest was colorless.

To the combined water fractions, cooled below 20°, 200 g. of potassium carbonate was added, and the upper layer combined with the rest of the 1,3-dioxepane. The 1,3-dioxepane, cooled below 20°, was washed with 300 g., then 200 g. of cold 40% sodium hydroxide solution (more water may be added if needed to dissolve insolubles), and dried with 20 g. sodium hydroxide pellets and 100 g. anhydrous sodium sulfate.

The 1,3-dioxepane was put in a still pot, 20–30 g. of sodium was added, and the mixture was distilled at atmospheric pressure. If alkali is not present, reduced pressure (<150 mm.) is required for this distillation. The products were 80 g. (3%) of tetrahydrofuran and 3090 g. (90%) of 1,3-dioxepane, b.p. 119° at atmospheric pressure or 70° at 150 mm.

1,3-Dioxep-5-ene was made by the same general method as 1,3-dioxepane except that near the end of the initial distillation, during water addition, the pot temperature rose rapidly to about 350° leaving a large tarry residue in the flask. This reaction should be carried out in a hood behind a safety shield.

5,6-Dibromo-1,3-dioxepane. To a solution of 100 g. 1,3-dioxep-5-ene (1.0 mole) in 700 ml. chloroform cooled to −55°, there was added dropwise with rapid stirring a solution of 140 g. bromine (0.875 mole) in 700 ml. chloroform during 3 hr., during which time the yellow color completely disappeared. At 0°, the colorless solution was washed with 300 ml. of 10% sodium sulfite, and then washed twice with 200 ml. water. Chloroform was removed by evaporation under reduced pressure below 50°. The residue, 5,6-dibromo-1,3-dioxepane, weighed 231 g. (101%) and on standing became a mass of white crystals with a trace of oil. Recrystallization from petroleum ether gave fine white needles, m.p. 39–40°.

Anal. Calcd. for $C_5H_8Br_2O_2$: C, 23.05; H, 3.08; Br, 61.58. Found: C, 22.85; H, 3.25; Br, 61.50.

5,6-Dichloro-1,3-dioxepane. To a solution of 117 g. 1,3-dioxep-5-ene (1.17 moles) in 700 ml. chloroform cooled to −55, there was added dropwise a solution of 82 g. chlorine

(3) J. W. Hill and W. H. Carothers, *J. Am. Chem. Soc.*, **57**, 926 (1935).

(4) H. S. Hill and H. Hibbert, *J. Am. Chem. Soc.*, **45**, 3115 and 3130 (1923).

(5) German Patent 805,520, to Badische Aniline and Soda Fabrik, May 21, 1951.

(6) A. Hinz, G. Meyer, and G. Schücking, *Ber.*, **76B**, 687 (1943).

(7) M. M. Sprung and F. O. Guenther, *J. Am. Chem. Soc.*, **73**, 1884 (1951).

(8) E. T. McBee, W. F. Marzluff, and O. R. Pierce, *J. Am. Chem. Soc.*, **74**, 444–6 (1952).

(1.17 moles) dissolved in 700 ml. chloroform during 1 hr. at −50°. The solution was kept 1 hr. at −50° and warmed gradually over 2 hr. to −10°C. The liquid was washed with 300 ml. of 10% sodium sulfite, twice with water, and dried over anhydrous sodium sulfate. After evaporating chloroform, 151 g. (75%) of colorless 5,6-dichloro-1,3-dioxepane boiling at 56° at 1 mm. was obtained.

Anal. Calcd. for $C_5H_8Cl_2O_2$: C, 35.12; H, 4.68; Cl, 41.50. Found: C, 40.75; H, 5.00; Cl, 40.75.

2-Hexyl-1,3-dioxep-5-ene. A mixture of 114 g. *n*-heptaldehyde (1.0 mole), 88 g. 2-butenediol-1,4 (1.0 mole), and 0.2 g. *p*-toluenesulfonic acid was heated gradually to 150°. The distillate had two layers. The lower aqueous fraction was discarded, and the upper *n*-heptaldehyde fraction was returned to the still pot. After water evolution became slow the pressure was lowered gradually to 2 mm., keeping the oil bath temperature 150°, and the distillate was dried over sodium sulfate. Redistillation gave some low-boiling fractions and 98 g. (53%) of 2-hexyl-1,3-dioxep-5-ene, boiling at 93° at 2 mm.

WILMINGTON 98, DEL.

[COMMUNICATION NO. 1873 FROM THE KODAK RESEARCH LABORATORIES]

By-products of the Willgerodt Reaction Applied to α- and γ- Picoline

P. E. MILLER, G. L. OLIVER, J. R. DANN, AND J. W. GATES, JR.

Received December 13, 1956

An additional by-product of the Willgerodt reaction of aniline, γ-picoline, and sulfur has been identified as *N,N'*-diphenylisonicotinamidine and its structure confirmed by independent synthesis. The structure of 2-(4-pyridyl)benzothiazole also obtained in this reaction has been confirmed by an independent synthesis. The Willgerodt reaction of aniline, α-picoline, and sulfur produced 2-(2-pyridyl)benzothiazole, *N,N'*-diphenylpicolinamidine and the expected thiopicolinanilide.

In order to obtain 2-(4-pyridyl)benzothiazole (I) from readily available materials, the reaction of γ-picoline, aniline, and sulfur at elevated temperatures, as reported by Porter,[1] was carried out by a similar procedure but at 180–220°. The reaction product after distillation melted at 120–160° instead of 126–130° and, after recrystallization from alcohol, still melted in this same range. It was found that a separation into two materials, one melting at 133–135° (I) and the other melting at 194–196° (II) could be accomplished by extracting with ligroin, in which the low melting material was soluble.

The lower melting product was the desired 2-(4-pyridyl)benzothiazole, as reported and as synthesized by an independent method. Following the method as described in the literature[2] for the reaction of *o*-aminobenzenethiol with aldehydes and ketones, 2-(4-pyridyl)benzothiazoline (V) was prepared by the reaction of *o*-aminobenzenethiol (III) and 4-pyridinecarboxaldehyde (IV). Subsequent oxidation of (V) by ferric chloride produced the desired benzothiazole (I). The higher melting material (II) contained only carbon, nitrogen, and hydrogen; its molecular weight was found to be 281.

At the time of this investigation, we were unaware of the publication of Emmert and Holz[3] reporting the isolation of *N,N'*-diphenylisonicotinamidine from the reaction of γ-picoline, sulfur and either nitrobenzene or aniline under vigorous reflux. This reference was pointed out to us by H. D. Porter. The high melting material (II) was found to be the amidine derivative; its structure was confirmed by an independent synthesis following the procedure of Gerhardt,[4] for the preparation of *N,N'*-diphenylbenzamidine as outlined in Chart I.

When α-picoline, aniline, and sulfur were heated at 180–220° for 12 hr. instead of at 160° as reported,[1] the thiopicolinanilide (VIII) was obtained, but 2-(2-pyridyl)benzothiazole (X)[5] and *N,N'*-diphenylpicolinamidine (IX) were also isolated among the products of the reaction. The structures of these products were confirmed as outlined in Chart II.

EXPERIMENTAL

2-(4-Pyridyl)benzothiazole (I) *and N,N'-diphenylisonicotinamidine* (II). A suspension of 96.2 g. (3.0 g. atom) of sulfur, 93.1 g. (1.0 mole) of γ-picoline and 139.7 g. (1.5 moles) of aniline was heated under reflux for 24 hr., the inner temperature rising from 180 to 220°. The unreacted aniline and γ-picoline were removed by distillation under a vacuum at 7 mm. and, on continuing the distillation, the material boiling at 198–220° (7 mm.) was collected. On recrystallization from absolute alcohol, the distillate consisted of a yellow, crystalline material, m.p. 120–160°. An alternate method consisted in removing the unreacted aniline and γ-picoline by distillation under a vacuum and crystallizing the tarry residue out of absolute alcohol; the yellow crystalline material again melted at 120–160°; and distillation, b.p. 200–210° at 2 mm., as well as subsequent recrystallization from absolute alcohol, did not alter the melting point range. Extraction of this material for 16 hr. in a Soxhlet extractor with ligroin (b.p. 65–75°) produced a soluble frac-

(1) H. D. Porter, *J. Am. Chem. Soc.*, **76**, 127 (1954).

(2) A. W. Hofmann, *Ber.*, **13**, 1236 (1880); M. Claasz, *Ber.*, **45**, 1031 (1912); M. T. Bogert and A. Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925); H. P. Larkelma and P. X. Sharnoff, *J. Am. Chem. Soc.*, **53**, 2654 (1931).

(3) B. Emmert and A. Holz, *Chem. Ber.*, **87**, 676 (1954).

(4) C. Gerhardt, *Ann.*, **108**, 219 (1858).

(5) B. Emmert and M. Groll, *Chem. Ber.*, **86**, 208 (1953).

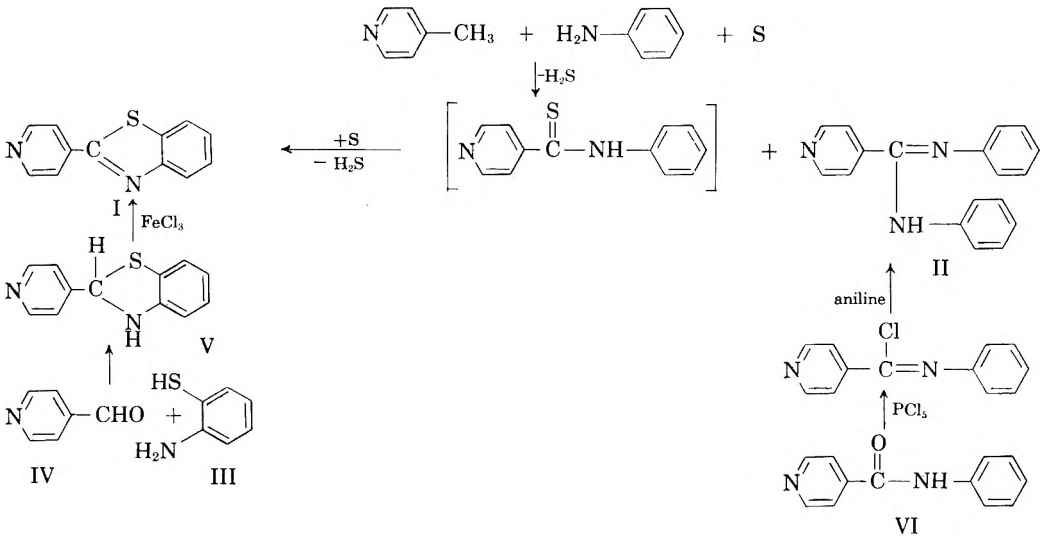


Chart I

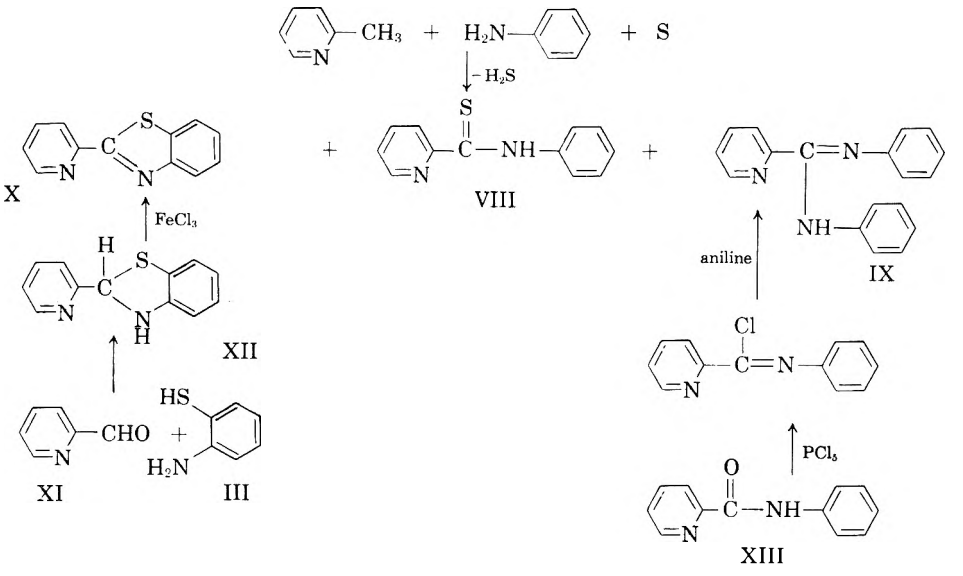


Chart II

tion from which the 2-(4-pyridyl)benzothiazole (I), m.p. 133–134°, was isolated from absolute alcohol (yield, 28–36 g.).

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.9; H, 3.8; N, 13.2; S, 15.1. Found: C, 68.0; H, 3.9; N, 13.1; S, 14.7.

The material II which was insoluble in ligroin was also crystallized from absolute alcohol, m.p. 194–196°, yield, 24–30 g.

Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.1; H, 5.5; N, 15.4; mol. wt. 273. Found: C, 79.3; H, 5.6; N, 15.1; mol. wt. 281 (ebullioscopic in absolute alcohol).

2-(4-Pyridyl)benzothiazoline hydrochloride (V). Into a solution of 2.5 g. (0.02 mole) of *o*-aminobenzenethiol in 30 ml. of absolute alcohol was passed an equimolar amount of hydrogen chloride gas (0.73 g.). A vigorous reaction ensued as 2.14 g. of 4-pyridinecarboxaldehyde (from the Aldrich Chemical Co.) was added to the warm solution. Bright-yellow crystals separated from the orange-brown solution on cooling. On recrystallization from alcohol, 4.2 g. of the benzothiazoline salt was obtained, m.p. 192°.

Anal. Calcd. for $C_{12}H_{11}ClN_2S$: C, 57.47; H, 4.42; N, 11.17. Found: C, 57.6; H, 4.0; N, 11.3.

2-(4-Pyridyl)benzothiazole (I). An aqueous solution of 1.0 g. (0.004 mole) of the benzothiazoline and 1.3 g. (0.008 mole) of anhydrous ferric chloride was heated about 15 min., cooled, and filtered. The precipitate was recrystallized from a small volume of alcohol, giving needles, m.p. 133–135°. (Lit. 131–132°.[1]) A mixed melting point with a sample from the Willgerodt reaction showed no depression.

Reaction of isonicotinic acid with thionyl chloride and aniline. Thirty-eight g. (0.33 mole) of thionyl chloride was added to 12.3 g. (0.1 mole) of isonicotinic acid in a 250-ml. round-bottomed flask, equipped with a Claisen head and a condenser. After the first vigorous reaction had subsided, the mixture was warmed on the steam bath for 30 min. The excess thionyl chloride was removed at 3 mm. pressure with gentle warming on the steam bath. The residue was cooled and 9.30 g. (0.1 mole) of aniline in 100 ml. of benzene was added. The reaction mixture was heated on the steam bath for 1 hr., cooled, and filtered. One half of the crude precipitate was dissolved in 100 ml. of cold water, filtered, and 5% sodium hydroxide was added until the *p*H reached 7.0. The white precipitate which formed was filtered and washed with water to give 5.7 g. (57.5%) of isonicotinanilide VI), m.p. 170–172°. Recrystallization from absolute alcohol did not change the melting point.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.6; H, 5.5; N, 14.1. Found: C, 73.0; H, 5.2; N, 14.2.

Reaction of isonicotinanilide hydrochloride with phosphorus pentachloride and aniline. One half of the crude isonicotinanilide hydrochloride described in a preceding section (0.0288 mole) in 50 ml. of dry benzene was heated to 50° in a round-bottomed flask and 20 g. of phosphorus pentachloride was added slowly. The reaction mixture was then heated to 140° for 1 hr., all of the solvent distilling off. Aniline (0.1 mole) in 100 ml. of benzene was then added to the residue and the reaction mixture was heated on the steam bath for 45 min. and 10 ml. more of aniline was added. The mixture was cooled and filtered, the precipitate was taken up in 10% hydrochloric acid, treated with Norit, filtered, and taken to *p*H 4.0 with 5% sodium hydroxide. The precipitate which formed was recrystallized from ethyl alcohol to give 0.9 g. (10.4%) of *N,N'*-diphenylisonicotinamidine, melting at 192–193° (Fisher-Johns). A mixed melting point with the product from the Willgerodt reaction was not depressed.

Thiopicolinanilide (VIII); *2-(2-pyridyl)benzothiazole* (X); *and N,N'-diphenylpicolinamidine* IX. A suspension of 96.2 g. (3.0 g. atom) of sulfur, 93.1 g. (1.0 mole) of α-picoline, and 139.7 g. (1.5 moles) of aniline was heated under reflux for 16 hr., the inner temperature rising from 180–220°. The unreacted aniline and α-picoline were removed by distillation under a vacuum. Excess sulfur was removed by solution of the pot residue in 1500 ml. of alcohol, cooling, and filtering. The filtrate, after concentration to 600 ml. and chilling, deposited 15 g. of yellow crystals, m.p. 126–133°. One recrystallization out of alcohol gave a material, m.p. 133–135°; the mixed melting point with 2-(2-pyridyl)benzothiazole was not depressed.

After removal of the benzothiazole, the filtrate was concentrated and distilled under a vacuum at 1 mm. to give the following fractions:

(1) b.p. 140–170° (96 g.)
(2) b.p. 170–176° (54 g.)
(3) b.p. 176–185° (with slight decomposition) 8 g.

The first fraction, upon solution in warm alcohol (40°), yielded two crystalline solids: 2-(2-pyridyl)benzothiazole, m.p. 126–133°, 45 g., only slightly soluble in alcohol, and thiopicolinanilide, m.p. 51–53° (42 g.), which is more soluble and crystallized from the filtrate upon chilling.

The second fraction, upon solution in alcohol and chilling, yielded thiopicolinanilide, m.p. 51–53°.

The third fraction, upon solution in alcohol and chilling, yielded *N,N'*-diphenylpicolinamidine (IX), m.p. 93–95°, after recrystallization from absolute alcohol and ligroin.

Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.1; H, 5.5; N, 15.4; mol. wt., 273. Found: C, 79.4; H, 5.6; N, 15.1; mol. wt., 284.

2-(2-Pyridyl)benzothiazoline hydrochloride (XII). This isomer was prepared by the method just described for compound V from 2-pyridinecarboxaldehyde (Aldrich Chemical Co.). The bright yellow crystals melted, with decomposition, at 166–168°.

Anal. Calcd. for $C_{12}H_{11}ClN_2S$: C, 57.47; H, 4.42; N, 11.17. Found: C, 57.9; H, 4.4; N, 11.5.

2-(2-Pyridyl)benzothiazole (X). The oxidation of the benzothiazoline was accomplished by the procedure just described for compound I to give the benzothiazole, m.p. 133–135°. A mixed melting point with a sample from the Willgerodt reaction showed no depression.

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.90; H, 3.80; N, 13.20. Found: C, 67.9; H, 3.8; N, 13.2.

N,N'-Diphenylpicolinamidine (IX). Picolinanilide XIII, m.p. 72–74° was prepared by the method of Engler.[6] A suspension of 6.6 g. of picolinanilide in 25 ml. of dry benzene was treated with 10 g. of phosphorus pentachloride at 50°. The reaction mixture was then heated to 110° for 3 hr., all of the solvent distilling off. Aniline (10 ml.) in 60 ml. of dry benzene was then added to the residue and the reaction mixture was heated on the steam bath for 1 hr. The mixture was cooled, filtered, and the precipitate was dissolved in 100 ml. of 10% hydrochloric acid. This solution was treated with carbon, filtered, and taken to *p*H 6.0 with 10% sodium hydroxide solution. Upon cooling, a precipitate was formed which was recrystallized from alcohol, m.p. 93–95°. A mixed melting point with the product from the Willgerodt reaction was not depressed.

ROCHESTER 4, N. Y.

(6) C. Engler, *Ber.*, **27**, 1786 (1894).

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Tritylation of Some Phenols and Naphthols

NG. PH. BUU-HOÏ AND RICHARD RIPS

Received December 26, 1956

The Baeyer-Villiger condensation reaction of triphenylcarbinol with some phenols, naphthols, and dihydroxynaphthalenes is investigated, and the constitution of several of the resulting substitution products is discussed.

The Baeyer-Villiger condensation of triphenylcarbinol with phenols, phenol ethers, and naphthols to give tritylated products was extensively investigated by Hardy,[1] who found that condensation occurred only in the position *para* to a phenol or an ether group. In the case of β-naphthol, however, Hardy assigned the structure of 1-trityl-2-naphthol (I) to the monotritylated product, without offering any proof of constitution. Recently, Schönberg, Mustafa, and Shalaby[2] reported an unequivocal synthesis of 1-trityl-2-naphthol by reacting phenylmagnesium bromide with *o*-naphthofuchsone; the reaction product, m.p. 155°, differed from Hardy's substance, which melted at 228°. This observation led us to investigate anew the tritylation reaction of phenolic compounds, to ascertain whether there would be true instances of *ortho* substitution.

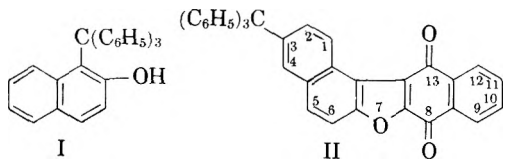
Repetition of Hardy's experiments with β-naphthol gave a tritylnaphthol melting at 230°, which condensed readily with 2,3-dichloro-1,4-naphthoquinone in pyridine to give a furanoquinone. This reaction proved that the position 1 adjacent to the hydroxy group was free,[3] thus confirming Schön-

(1) Hardy, *J. Chem. Soc.*, 1000 (1929).

(2) Schönberg, Mustafa, and Shalaby, *J. Am. Chem. Soc.*, **77**, 5756 (1955).

(3) *Cf.* Buu-Hoï, *J. Chem. Soc.*, 489 (1952); Buu-Hoï and Demerseman, *J. Chem. Soc.*, 4699 (1952).

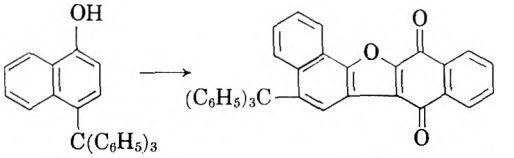
berg, Mustafa, and Shalaby's observations. Apart from position 1, the trityl group could have entered



I II

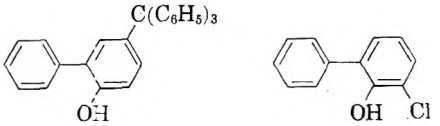
position 6 or 8; in view of similar results obtained in *tert.* alkylations[4] and cyclohexylation[5] of β-naphthol, the most probable structure of Hardy's compound is 6-trityl-2-naphthol, and that of the corresponding furanoquinone, 3-trityldinaphtho[2,1-2′,3′]furan-8,13-dione (II). These structures are further upheld by the failure of 6-bromo-2-naphthol to undergo tritylation.

In the reaction of triphenylcarbinol with α-naphthol, Hardy isolated a monosubstitution product which he formulated as 4-trityl-1-naphthol (III); because of the known ability of α-naphthol to undergo some degree of alkylation in position 2,[5] this formula needed some confirmation. This was now forthcoming in a successful condensation with 2,3-dichloro-1,4-naphthoquinone to a furanoquinone, which must be 5-trityldinaphtho[1,2-2′,3′]furan-7,12-dione (IV).



III IV

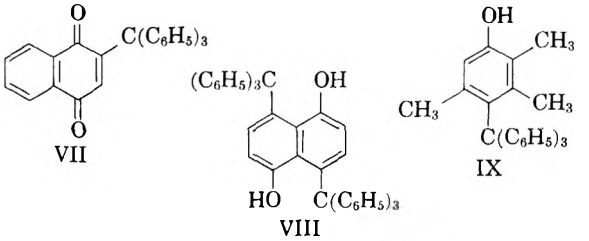
The resistance of trityl radicals to *ortho* substitution in Baeyer-Villiger reactions, already found by Hardy in several examples in the benzene series, was now further demonstrated in the biphenyl series by the behavior of 2- and 4-hydroxybiphenyl. The former compound readily yielded 2-hydroxy-5-tritylbiphenyl (V), while the latter failed to react; it is true that the reaction also failed with 6-chloro-



V VI

2-hydroxybiphenyl (VI), despite the presence of a free *para* position, but this could probably be attributed to the deactivating influence of the chlorine atom.

It does not ensue from the previously recorded failures that *ortho* substitution cannot take place in certain favorable circumstances. 1,4-Dihydroxynaphthalene, for instance, could be tritylated, although the primary substitution product underwent oxidation in the course of the reaction, to give 2-trityl-1,4-naphthoquinone (VII); with 1,5-dihydroxynaphthalene, disubstitution occurred as expected, to give a compound considered to be 1,5-dihydroxy-4,8-ditritylnaphthalene (VIII). In the case of 2,7-dihydroxynaphthalene,[6] a disubstitution product was also obtained, in which at least one of



VII VIII IX

the trityl groups occupied an α-position, as no furanoquinone was formed with 2,3-dichloro-1,4-naphthoquinone.

The preferential attack on *para* positions in Baeyer-Villiger reactions involving triphenylcarbinol does not seem due to steric hindrance, as 2,3,5-trimethylphenol, a compound whose *para* position is sterically hindered, readily underwent tritylation, to give 2,3,5-trimethyl-4-tritylphenol (IX). It should be noted that the presence of carbonyl groups inhibits tritylation completely, as is the case with 2,4-dihydroxybenzaldehyde, gallacetophenone, and lawsone (2-hydroxy-1,4-naphthoquinone).

EXPERIMENTAL

Tritylation of β-naphthol. To a solution of 12 g. of triphenylcarbinol and 12 g. of β-naphthol in 120 ml. of warm acetic acid, 20 g. of sulfuric acid was added portionwise with stirring, and the mixture left for three days at room temperature. The abundant precipitate which had by then formed (in Hardy's experiments the reaction mixture was left for one month) was collected, washed thoroughly with aqueous ethanol, dried, and recrystallized from ethanol. *6(?)-Trityl-2-naphthol* (I) was thus obtained as fine, colorless prisms, m.p. 230°; yield, 6 g. A similar experiment, performed with 6-bromo-2-naphthol, failed to give any substitution product even after 1 month.

3(?)-Trityldinaphtho[2,1-2′,3′]furan-8,13-dione (II). A mixture of 3 g. of the foregoing naphthol, 1.8 g. of 2,3-dichloro-1,4-naphthoquinone, and 30 ml. of anhydrous pyridine was gently refluxed for 2 hr.; the precipitate which formed after cooling was collected, washed with aqueous ethanol, then with water, dried, and recrystallized from pyridine. Yield, 3 g. of silky golden-yellow needles, m.p. 347–348°, giving, with hot sulfuric acid, a greenish-blue coloration.

Anal. Calcd. for $C_{39}H_{24}O_3$: C, 86.7; H, 4.5. Found: C, 86.5; H, 4.5.

Tritylation of α-naphthol. A mixture of 13.5 g. of α-naphthol, 12 g. of triphenylcarbinol, and 120 ml. of warm acetic acid was treated with 20 g. of sulfuric acid and left

(4) Buu-Hoï, Le Bihan, Binon, and Rayet, *J. Org. Chem.*, **15**, 1060 (1950); Buu-Hoï, Le Bihan, and Binon, *J. Org. Chem.*, **16**, 185 (1951); Buu-Hoï, Le Bihan, Binon, and Xuong, *J. Org. Chem.*, **16**, 988 (1951).

(5) Alberti, *Ann.*, **450**, 309 (1926).

(6) For previous work on substitution reactions of 1,5- and 2,7-dihydroxynaphthalene, see Buu-Hoï and Lavit, *J. Chem. Soc.*, 1743 (1956); *J. Org. Chem.*, **20**, 1191 (1955).

overnight at room temperature. The yield was 14 g. of *4-trityl-1-naphthol*, crystallizing from ethanol in colorless prisms, m.p. 205°; this product, dissolved in hot ethanol, gave with ferric chloride a brown-violet coloration which faded on cooling.

Condensation of this naphthol with 2,3-dichloro-1,4-naphthoquinone in pyridine yielded *5-trityldinaphtho-[1,2-2',3]furan-7,12-dione* (IV), crystallizing from pyridine in silky golden yellow needles, m.p. 352–353°, giving, with sulfuric acid, a cobalt-blue halochromy; yield 80%.

Anal. Calcd. for $C_{39}H_{24}O_3$: C, 86.7; H, 4.5. Found: C, 86.3; H, 4.5.

2-Hydroxy-5-trityldiphenyl (V). A solution of 3 g. of 2-hydroxydiphenyl and 3 g. of triphenylcarbinol in 30 ml. of warm acetic acid was treated in the usual way with 5 g. of sulfuric acid, and the red mixture obtained was left for a week at room temperature. The precipitate (4 g.) was treated as above, and yielded on recrystallization from a mixture of benzene and ethanol, shiny, colorless, sublimable needles, m.p. 246–247°.

Anal. Calcd. for $C_{31}H_{24}O$: C, 90.3; H, 5.9. Found: C, 89.9; H, 6.1.

From similar experiments performed with 3-chloro-2-hydroxybiphenyl and 4-hydroxybiphenyl (1 month at room temperature), only the starting materials were recovered, along with some triphenylmethane.

2-Trityl-1,4-naphthoquinone (VII). A mixture of 3 g. of 1,4-dihydroxynaphthalene and 3 g. of triphenylcarbinol in 50 ml. of acetic acid was treated with 5 g. of sulfuric acid in the usual way. The precipitate (3 g.), obtained after 3 days on addition of water, was washed with water, and crystallized several times from a mixture of ethanol and benzene, to give *2-trityl-1,4-naphthoquinone* in the form of canary yellow prisms, m.p. 222–223°, giving a deep green coloration in sulfuric acid. This compound was insoluble in aqueous alkalis, and yielded phthalic acid on oxidation with potassium permanganate.

Anal. Calcd. for $C_{29}H_{20}O_2$: C, 87.0; H, 5.0. Found: C, 87.2; H, 5.2.

1,5-Dihydroxy-4,8-ditritylnaphthalene (VIII). A mixture of 3 g. of 1,5-dihydroxynaphthalene and 6 g. of triphenylcarbinol in 60 ml. of acetic acid was treated with 5 g. of sulfuric acid. The precipitate which formed after 2 days was washed with ethanol, then with hot dioxane, and recrystallized from tetralin, giving 3 g. of fine, colorless prisms, m.p. 429–430°.

Anal. Calcd. for $C_{48}H_{36}O_3$: C, 89.4; H, 5.6. Found: C, 89.2; H, 5.9.

2,7-Dihydroxy-1,x-ditritylnaphthalene. This compound, prepared from 2,7-dihydroxynaphthalene as for β-naphthol, crystallized from a mixture of ethanol and benzene in silky colorless needles, m.p. 318–320°; yield 60%.

Anal. Calcd. for $C_{48}H_{36}O_2$: C, 89.4; H, 5.6. Found: C, 89.1; H, 5.9.

This compound failed to give a furanoquinone on heating with 2,3-dichloro-1,4-naphthoquinone in pyridine medium.

2,3,5-Trimethyl-4-tritylphenol (IX). Prepared from 2,3,5-trimethylphenol (3 g.), this compound crystallized from ethanol in silky colorless needles (1 g.), m.p. 170–171°.

Anal. Calcd. for $C_{28}H_{26}O$: C, 88.9; H, 6.9. Found: C, 88.6; H, 6.6.

Similar experiments performed with *p-tert.* amylphenol, 2,4-dihydroxybenzaldehyde, gallacetophenone, and lawsone were completely negative.

PARIS (V^e^), FRANCE

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Friedel-Crafts Acylations of 3-Chloro-4-methoxybiphenyl

NG. PH. BUU-HOÏ, MICHEL SY, AND JEAN RICHÉ

Received December 26, 1956

Friedel-Crafts acylations of 3-chloro-4-methoxybiphenyl with aliphatic and aromatic acid chlorides are shown to give 4'-acyl-3-chloro-4-methoxybiphenyls, several of which were prepared and their reactions investigated. In the course of this work, a large number of new derivatives of 3-chloro-4-hydroxybiphenyl and its methyl ether (ketones, phenols, quinolines) were synthesized.

Substitution reactions in the biphenyl series present an interesting subject of research, because of the possibility for substitutions to be homonuclear or heteronuclear. For instance, 4-methoxybiphenyl has been shown to undergo Friedel-Crafts acylations[1] mainly at position 4', with some substitution at position 3. When the directing effect of the first substituent is weaker, as is the case with 4-alkyldiphenyls,[2] acylations have been found to occur almost exclusively at position 4'. It was now thought of interest to investigate similar Friedel-Crafts reactions with 3-chloro-4-methoxybiphenyl (I), a readily accessible molecule in which the position *ortho* to the methoxy group is deactivated by the chlorine atom present in the *meta* position. (It is known that bromination of 4-hydroxybiphenyl leads to a monobromo derivative, even in relatively drastic conditions.)[3]

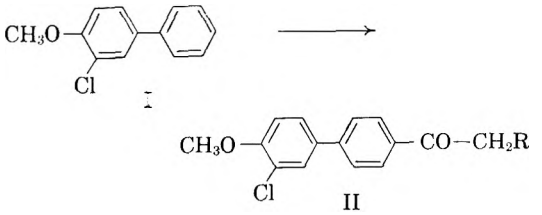
The starting material, 3-chloro-4-hydroxybiphenyl, possesses to some extent the properties of a cryptophenol, and could be completely methylated with sodium hydroxide and dimethyl sulfate only in the presence of methanol or ethanol;[4] acylation of 3-chloro-4-methoxybiphenyl by acetyl chloride in the presence of aluminum chloride in nitrobenzene medium gave, in excellent yields, a ketone which must have been 4'-acetyl-3-chloro-4-methoxybiphenyl (II; R = H), as its demethylation afforded a substance which, since it did not show the proper-

(1) See Fieser and Bradsher, *J. Am. Chem. Soc.*, **58**, 1738, 2337 (1936).

(2) Buu-Hoï and Royer, *Rec. trav. chim.*, **70**, 825 (1951); *Bull. soc. chim. France*, **17**, 489 (1950).

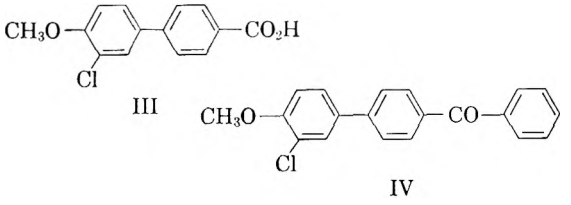
(3) Bell and Robinson, *J. Chem. Soc.*, 1132 (1927).

(4) For other instances of methylation of cryptophenols, see Buu-Hoï and Lavit, *J. Chem. Soc.*, 2412 (1956).



II

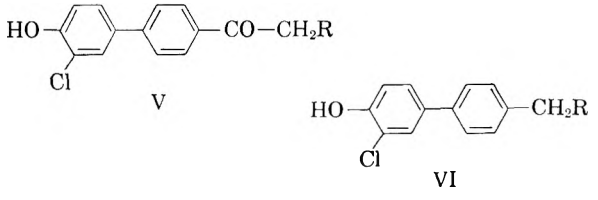
ties of an *o*-hydroxy ketone, must have been the expected 4′-acetyl-3-chloro-4-hydroxybiphenyl. No appreciable amount of an isomeric ketone could be isolated, and this confirms the theoretical prediction concerning the deactivation of position 5 by the chlorine atom occupying position 3. Replacement of acetyl chloride by propionyl, *n*-butyryl, and phenacetyl chloride yielded 3-chloro-4-methoxy-4′-propionyl- (II; R = C_2H_5), 3-chloro-4-methoxy-4′-*n*-butyryl- (II; R = *n*-C_3H_7), and 3-chloro-4-methoxy-4′-phenacetylbiphenyl (II; R = $CH_2C_6H_5$), respectively. In the case of benzoyl chloride, the ketone obtained was 4′-benzoyl-3-chloro-4-methoxybiphenyl (IV), as it was identical with the product of a Friedel-Crafts reaction between benzene and the chloride of 3-chloro-4-methoxybiphenyl-4′-carboxylic acid (III); this acid was prepared by sodium hypobromite oxidation of 4′-acetyl-3-chloro-4-methoxybiphenyl. This proof of constitution was thought useful, in view of the differences



III IV

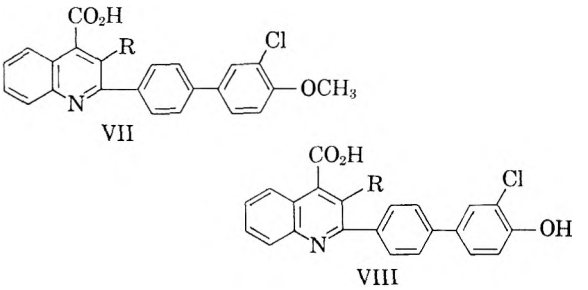
observed between aliphatic acid chlorides and nuclear aromatic acid chlorides in respect of orientation in Friedel-Crafts acylations.[5]

Demethylation of the ketones of general formula II by means of pyridine hydrochloride[6] readily yielded the corresponding 4′-acyl-3-chloro-4-hydroxybiphenyls (V), which showed pronounced bacteriostatic activity against several germs (tubercle bacilli, staphylococci, etc.).[7] Kishner-Wolff reduction of 4′-acyl-3-chloro-4-methoxybiphenyls, using the Huang-Minlon technique,[8] readily gave the corresponding 4′-alkyl- and 4′-arylalkyl-3-chloro-4-methoxybiphenyls; demethylation of these ethers yielded 4′-alkyl- and 4′-arylalkyl-3-chloro-4-hydroxybiphenyls of general formula VI, which also showed antibacterial properties.



V VI

The ready availability of ketones of type II prompted an investigation of their Pfitzinger reactions with isatin. In several previous papers, it had been pointed out that this type of reaction is highly sensitive to steric hindrance,[9] and this was again found to be the case. Thus, in ethanol medium, isatin reacted with 4′-acetyl- and 4′-propionyl-3-chloro-4-methoxybiphenyl to give in 85–90% yield 2-(3-chloro-4-methoxy-4′-xenyl)cinchoninic acid (VII; R = H) and its 3-methyl derivative (VII; R = CH_3) after 68 hr., while 4′-*n*-butyryl-3-chloro-4-methoxybiphenyl gave only 18% yield of 3-ethyl-2-(3-chloro-4-methoxy-4′-xenyl)cinchoninic acid (VII; R = C_2H_5) after 120 hrs. The corresponding hydroxy cinchoninic acids (VIII), which could not be synthesized by the Pfitzinger reaction with 4′-acyl-3-chloro-4-hydroxybiphenyls, were prepared by pyridine hydrochloride-demethylation of the methoxy acids (VII). Thermal decomposition of these latter acids gave the corresponding 2-(3-chloro-4-methoxy-4′-xenyl)quinolines.



VII VIII

EXPERIMENTAL

4′-Acetyl-3-chloro-4-methoxybiphenyl (II; R = H). Into an ice-cooled solution of 3-chloro-4-methoxybiphenyl (1 mole; prepared by methylation of commercial 3-chloro-4-hydroxybiphenyl with dimethyl sulfate and sodium hydroxide in aqueous ethanol) and acetyl chloride (1.2 moles) in dry carbon disulfide, finely powdered aluminum chloride (1.1 moles) was stirred portionwise, and the mixture left overnight at room temperature. The reaction mixture was then treated with ice-cooled hydrochloric acid, the carbon disulfide layer was washed with aqueous sodium carbonate, then with water, and dried over sodium sulfate. The solvent was distilled and the oily residue fractionated under reduced pressure. Yield: 88% of a *ketone*, b.p. 244–246°/15 mm., which crystallized from ethanol in shiny colorless needles, m.p. 109°.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.1; H, 5.0. Found: C, 69.1; H, 5.1.

(5) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).
(6) Buu-Hoï, *Rec. trav. chim.*, **68**, 759 (1949).
(7) Unpublished results.
(8) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946); **71**, 3301 (1949); Buu-Hoï, Hoán, and Xuong, *Rec. trav. chim.*, **71**, 285 (1952).
(9) Buu-Hoï and Cagniant, *Rec. trav. chim.*, **62**, 519, 713 (1943); **64**, 214 (1945); *Bull. soc. chim. France*, **13**, 123, 134 (1946); Buu-Hoï, *J. Chem. Soc.*, 795 (1946); Buu-Hoï and Royer, *Bull. soc. chim. France*, **13**, 374 (1946); **17**, 489 (1950); *J. Chem. Soc.*, 106 (1948); *Rec. trav. chim.*, **70**, 825 (1951); Buu-Hoï, Royer, Xuong, and Jacquignon, *J. Org. Chem.*, **18**, 1209 (1953).

TABLE I

4′-SUBSTITUTED DERIVATIVES OF 3-CHLORO-4-HYDROXYBIPHENYL

Acetyl group	Formula	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
4′-Acetyl-	$C_{14}H_{11}ClO_2$	143	68.2	4.5	68.2	4.2
4′-Propionyl-	$C_{15}H_{13}ClO_2$	139–140	69.1	5.0	69.2	5.0
4′-Benzoyl-	$C_{19}H_{13}ClO_2$	151	73.9	4.2	73.7	4.3
4′-Phenacetyl-	$C_{20}H_{15}ClO_2$	208	74.4	4.7	74.2	4.4
4′-Ethyl-	$C_{14}H_{13}ClO$	97	72.3	5.6	72.3	5.7
4′-*n*-Propyl-	$C_{15}H_{15}ClO$	104	73.0	6.1	72.9	6.1

TABLE II

QUINOLINE DERIVATIVES

Substance	Formula	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
2-(3-Chloro-4-methoxy-4′-xenyl)-cinchoninic acid	$C_{23}H_{16}ClNO_3$	283–284	70.9	4.1	70.6	4.0
2-(3-Chloro-4-methoxy-4′-xenyl)-quinoline[a]	$C_{22}H_{16}ClNO$	221	76.4	4.6	76.3	4.5
2-(3-Chloro-4-hydroxy-4′-xenyl)-cinchoninic acid	$C_{22}H_{14}ClNO_3$	316	70.3	3.7	70.0	3.5
2-(3-Chloro-4-methoxy-4′-xenyl)-3-methylcinchoninic acid	$C_{24}H_{18}ClNO_3$	325	71.4	4.5	71.5	4.4
2-(3-Chloro-4-methoxy-4′-xenyl)-3-methylquinoline	$C_{23}H_{18}ClNO$	183	76.8	5.0	76.6	5.1
2-(3-Chloro-4-hydroxy-4′-xenyl)-3-methylcinchoninic acid	$C_{23}H_{16}ClNO_3$	371	70.9	4.1	70.8	4.0
2-(3-Chloro-4-methoxy-4′-xenyl)-3-ethylcinchoninic acid	$C_{25}H_{20}ClNO_3$	307	71.9	4.8	71.6	4.6
2-(3-Chloro-4-methoxy-4′-xenyl)-3-ethylquinoline	$C_{24}H_{20}ClNO$	136	77.1	5.4	77.0	5.4
2-(3-Chloro-4-hydroxy-4′-xenyl)-3-ethylcinchoninic acid	$C_{24}H_{18}ClNO_3$	331	71.4	4.5	71.1	4.4
2-(3-Chloro-4-methoxy-4′-xenyl)-3-phenylcinchoninic acid[b]	$C_{29}H_{20}ClNO_3$	309	74.8	4.3	74.7	4.1
2-(3-Chloro-4-methoxy-4′-xenyl)-3-phenylquinoline	$C_{28}H_{20}ClNO$	172	79.7	4.7	79.6	4.8
2-(3-Chloro-4-hydroxy-4′-xenyl)-3-phenylcinchoninic acid	$C_{28}H_{18}ClNO_3$	344–346	74.4	4.0	74.1	3.9
2-(3-Chloro-4-hydroxy-4′-xenyl)-3-phenylquinoline	$C_{27}H_{18}ClNO$	220	79.5	4.4	79.3	4.3

[a] The quinolines were prepared by heating the corresponding cinchoninic acids above their melting points, and crystallizing the residue from a mixture of benzene, to give colorless prisms. [b] Obtained in 80% yield.

TABLE III

4′-ALKYL AND 4′-ARYLALKYL DERIVATIVES OF 3-CHLORO-4-METHOXYBIPHENYL

Alkyl group	Formula	M.P. °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
4′-Ethyl-	$C_{15}H_{15}ClO$	72	73.0	6.1	72.9	6.3
4′-*n*-Propyl-	$C_{16}H_{17}ClO$	64	73.7	6.5	73.5	6.5
4′-*n*-Butyl-	$C_{17}H_{19}ClO$	52	74.3	6.9	74.3	7.0
4′-Benzyl-[a]	$C_{20}H_{17}ClO$	88	77.8	5.5	77.5	5.5
4′-(β-Phenylethyl)-	$C_{21}H_{19}ClO$	92	78.1	5.9	78.0	5.8

[a] Demethylation yielded a compound m.p. 82°.

The corresponding *semicarbazone* crystallized from a mixture of benzene and ethanol in shiny colorless prisms, m.p. 254°.

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: N, 13.2. Found: N, 12.9.

Chalcones derived from 4′-acetyl-3-chloro-4-methoxybiphenyl. The *benzylidene derivative*, prepared with benzaldehyde in ethanol medium and in the presence of a few drops of 20% aqueous sodium hydroxide, crystallized from a mixture of benzene and ethanol in shiny yellowish leaflets, m.p. 157°, giving an orange coloration with sulfuric acid.

Anal. Calcd. for $C_{22}H_{17}ClO_2$: C, 75.8; H, 4.9. Found: C, 75.8; H, 4.8.

p-Methoxybenzilidene derivative, pale yellow leaflets, m.p. 145°, gave a bright red coloration with sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}ClO_3$: C, 72.9; H, 5.0. Found: C, 73.1; H, 5.0.

Piperonylidene derivative, pale yellow leaflets, m.p. 158°, gave a violet-red coloration with sulfuric acid.

Anal. Calcd. for $C_{23}H_{17}ClO_4$: C, 70.3; H, 4.3. Found: C, 70.3; H, 4.3.

2-Furfurylidene derivative, shiny yellow leaflets, m.p. 148°, gave a bright red coloration with sulfuric acid.

Anal. Calcd. for $C_{20}H_{15}ClO_3$: C, 70.9; H, 4.4. Found: C, 70.7; H, 4.5.

2-Thenylidene derivative, pale yellow needles, m.p. 165°, gave a red coloration with sulfuric acid.

Anal. Calcd. for $C_{20}H_{15}ClO_2S$: C, 67.7; H, 4.2. Found: C, 67.7; H, 4.2.

3-Chloro-4-methoxybiphenyl-4'-carboxylic acid (III). A fine suspension of 4'-acetyl-3-chloro-4-methoxybiphenyl (1 mole) in an aqueous solution of sodium hypobromite (1.2 moles) was shaken with some dioxane for 4 hr., then heated for 1 hr. on the water bath. After addition of sodium hydrogen sulfite and filtration, the filtrate was acidified with hydrochloric acid, and the precipitate washed with water and recrystallized from dioxane. Yield: 80% of fine colorless prisms, m.p. 280–281°.

Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.0; H, 4.2. Found: C, 63.7; H, 4.3.

The corresponding *amide* crystallized from ethanol in fine colorless needles, m.p. 243°.

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.2; H, 4.6. Found: C, 64.1; H, 4.9.

4'-Propionyl-3-chloro-4-methoxybiphenyl (II; R = CH_3). Prepared in 86% yield as for the lower homolog, this ketone, b.p. 260–262°/15 mm., crystallized from ethanol in lustrous colorless leaflets, m.p. 111°.

Anal. Calcd. for $C_{16}H_{15}ClO_2$: C, 69.9; H, 5.5. Found: C, 70.0; H, 5.5.

4'-n-Butyryl-3-chloro-4-methoxybiphenyl (II; R = C_2H_5). This ketone (65% yield), b.p. 272–274°/18 mm., crystallized from ethanol in colorless leaflets, m.p. 86°.

Anal. Calcd. for $C_{17}H_{17}ClO_2$: C, 70.7; H, 5.9. Found: C, 70.5; H, 6.1.

4'-Phenacetyl-3-chloro-4-methoxybiphenyl (II; R = C_6H_5). This ketone (65% yield), b.p. 332–334°/17 mm., crystallized from a mixture of benzene and ethanol in colorless prisms, m.p. 144°.

Anal. Calcd. for $C_{21}H_{17}ClO_2$: C, 74.9; H, 5.1. Found: C, 74.8; H, 5.3.

The *semicarbazone* crystallized from acetic acid in fine colorless prisms, m.p. 245°.

4'-Benzoyl-3-chloro-4-methoxybiphenyl (IV). (a) *From benzoyl chloride* the yield was 68% of a ketone, m.p. 310–315°/20 mm., which crystallized from a mixture of ethanol and benzene in long colorless needles, m.p. 138°.

Anal. Calcd. for $C_{20}H_{15}ClO_2$: C, 74.4; H, 4.7. Found: C, 74.1; H, 4.5.

(b) *From 3-chloro-4-methoxybiphenyl-4'-carboxylic acid.* This acid was converted into its chloride by means of thionyl chloride in benzene solution on the water bath. The solvent was then distilled off and replaced by more benzene, aluminum chloride was added with cooling, and the mixture was left overnight. After the usual treatment, a ketone was obtained in 75% yield, identical with the one prepared from benzyl chloride.

Pfitzinger reactions with ketones II. The appropriate ketone was condensed with isatin in the usual way, the duration of reaction being 68 hr. for ketones II; R = H and R = CH_3, 100 hr. for ketone II; R = C_6H_5, and 120 hr. for ketone II; R = C_2H_5. Crystallization was from nitrobenzene producing fine yellowish prisms.

Demethylation of methoxy ketones II. A mixture of one part of the appropriate 4'-acyl-3-chloro-4-methoxybiphenyl and six parts of redistilled pyridine hydrochloride was gently refluxed for 15 to 30 min., and the cooled reaction product treated with dilute hydrochloric acid; the precipitate obtained was collected, washed, and purified *via* its sodium salt. Recrystallization was from benzene.

Reduction of methoxy ketones II. A solution of the methoxy ketone (1 mole) and 95% hydrazine hydrate (4 moles) in diethylene glycol was heated for a few minutes to allow formation of the hydrazone; potassium hydroxide (same weight as the hydrazine hydrate) was added after cooling, and the mixture refluxed for 1 hr. with removal of water. After cooling, water was added, the reduction product was taken up in benzene, the benzene solution was washed first with dilute hydrochloric acid, then with water, and dried over sodium sulfate. The solvent was removed, and the residue vacuum-distilled. Crystallization was from ethanol. Yield: 80 to 85%.

PARIS (V^e), FRANCE

[CONTRIBUTION FROM THE RESEARCH DIVISION, AMERICAN CYANAMID COMPANY, BOUND BROOK LABORATORIES]

Pyrido[2,3,4,5-*lmn*]phenanthridine

W. L. MOSBY

Received November 13, 1956

The synthesis of pyrido[2,3,4,5-*lmn*]phenanthridine and its 5,10-dimethyl homolog is described.

The only pyrido[2,3,4,5-lmn]phenanthridines thus far described have been aryl derivatives. These have been obtained[1,2] in the preparation of the yellow vat dye flavanthrone, and in the synthesis of trypanocidal drugs.[3] An aluminum chloride-sodium chloride melt was used[1,2] to cyclize 2,2'-diphthalimidobiphenyl, although 10-benzamido-5-phenylphenanthridine cyclized readily upon treatment with phosphorus oxychloride in nitrobenzene.[3] The third synthesis employed[3] was the reduction and simultaneous cyclodehydration of 2,2'-diaroyl-6,6'-dinitrobiphenyls. By a modification of the first of these methods, we have now prepared the prototype of this ring system, and its dimethyl homolog.

A few simple modifications of Ullmann's synthesis[4] of 2,2'-dinitrobiphenyl permitted the convenient preparation of quantities of this material in

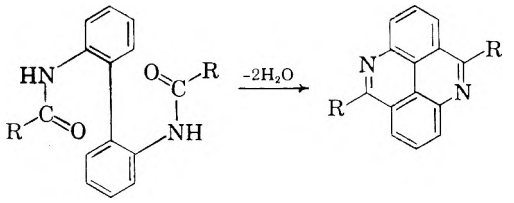
(1) F. Ebel, German Patent **614,196**; *Frdl.*, **22**, 1126 (1939); British Patent **431,790**; U. S. Patent **2,069,473**.

(2) V. Krepela and R. Štefec, *Collection Czechoslav. Chem. Commun.*, **9**, 29 (1937).

(3) A. E. S. Fairfull, D. A. Peak, W. F. Short, and T. I. Watkins, *J. Chem. Soc.*, 4700 (1952).

(4) F. Ullmann and J. Bielecki, *Ber.*, **34**, 2176 (1901).

about 71% yield. Stannous chloride has often[3,5,6] been used to reduce the nitro compound to 2,2′-diaminobiphenyl. Catalytic hydrogenation with palladium charcoal yielded the amine, but a product of better quality resulted from the neutral iron reduction of the dinitrobiphenyl. The diamine was converted to I and II by simply heating it to 150° in an open flask with, respectively, formic acid and acetic anhydride, and the yield and purity of the two products thus obtained were considerably improved over those previously described.



I (R = H)
II (R = CH_3)

III (R = H)
IV (R = CH_3)

Much time was spent finding conditions suitable for the cyclization of I and II to III and IV. The cyclization of the closely related 1-formamido-2-(2-formamidophenyl)naphthalene (under unspecified conditions) had been reported[7] unsuccessful. Treatment of I with (a) phosphorus oxychloride at 90°; (b) a mixture of phosphorus oxychloride, stannic chloride and nitrobenzene at reflux[8]; (c) polyphosphoric acid at 200° for 1 hr.; (d) an aluminum chloride–pyridine melt at 200° for 2 hr.; (e) an aluminum chloride–chlorobenzene slurry at reflux[9] for 2 hr., and (f) an aluminum chloride-sodium sulfite melt at 250° for 2 hr., each failed to produce detectible quantities of III. The best conditions found for the conversion of I and II to III and IV involve the use of a sodium chloride-aluminum chloride melt at 250° for 2 hr. Even with these conditions the yields are quite poor, and it is evident that the nature (aliphatic *vs.* aromatic, *etc.*) of the acyl group is a major factor in determining the yield of the pyrido[2,3,4,5-*lmn*]phenanthridine produced.

The ultraviolet absorption spectra of III and IV are essentially the same as that of pyrene with the exception that the "α" or "Group III" bands (350–370 mμ) are of much greater intensity than those of pyrene. This phenomenon is often encountered in comparing heterocyclic nuclei to their homocyclic analogs.[10] The curve of IV of course shows the expected slight bathochromic shift with respect to that of III.

Pyrido[2,3,4,5-*lmn*]phenanthridine proved surprisingly resistant to substitution by electrophilic reagents; it could not be nitrated or brominated in sulfuric acid solution although quinoline is readily nitrated[11] under these conditions. Attempts to oxidize III with hydrogen peroxide and a copper salt, conditions under which quinoline is converted to quinolinic acid,[12] were unsuccessful, and III was recovered unchanged.

EXPERIMENTAL[13]

2,2′-Dinitrobiphenyl. In a 3-necked flask equipped with a paddle stirrer, thermometer, and solid-addition funnel was placed 450 g. of 2-nitrochlorobenzene. This was melted and stirred at 240–245° while over a 2 hr. period 450 g. of copper powder (dust) was added in small portions. The mixture was then stirred for 2 hr. more at 250°, cooled somewhat, and poured into two liters of toluene. The solution was filtered, and the solids were washed well with toluene. The combined filtrate and washings were poured onto a 3″ × 18″ column of activated alumina. The first two liters of effluent contained only 6.1 g. of yellow oily impurities and were discarded. Several liters of toluene were then used to elute the product from the column. The eluate was stripped of solvent and the resulting solid was recrystallized once from benzene to give 220 g. (71% yield) of product, m.p. 119–122° (lit.[4] 124°).

2,2′-Diaminobiphenyl. A mixture of 60 g. of iron powder, 30 ml. of water and 2 ml. of acetic acid was stirred and boiled under reflux for 0.25 hr. Then 24.4 g. (0.10 mole) of powdered 2,2′-dinitrobiphenyl was added portionwise. During this addition a little ethanol was occasionally added (a total of 10 ml.). The resulting dark mixture was stirred and boiled under reflux for 5.5 hr., then cooled somewhat and 200 ml. of benzene was added, and the heating and stirring were continued for another hour. When the mixture had cooled, the benzene layer was decanted and the solids were washed well with additional benzene. The combined benzene extracts were dried with anhydrous potassium carbonate, treated with charcoal and filtered. The filtrate was stripped of solvent to give 18.0 g. (97.8% yield) of yellow crystalline product m.p. 75.4–77.6° (lit.[5,6] 79–80, 80–81°).

2,2′-Diformamidobiphenyl (I). A mixture of 92.0 g. of 2,2′-diaminobiphenyl and 80 ml. of 98% formic acid was heated in a flask equipped with a thermometer and a solvent "take-off" condenser. Water and formic acid distilled while the temperature of the residual liquid rose gradually to 150° where it was held for 0.5 hr. The melt was cooled, triturated with ethanol, then filtered and washed with ethanol and dried. The yield of crude product, m.p. 145.8–146.4° was 110.0 g. (91.7%). Two recrystallizations from methanol raised the melting point to 147.2–147.8° (lit.[5] 137°).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.00; N, 11.68. Found: C, 70.0; H, 4.93; N, 11.6.

2,2′-Diacetamidobiphenyl (II). A mixture of 18.4 g. of 2,2′-diaminobiphenyl, 10 ml. of acetic acid and 20 ml. of acetic anhydride was heated to 150° for 10 min., cooled and tri-

(5) St. v. Niementowski, *Ber.*, **34**, 3325 (1901).

(6) S. Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.*, **6**, 263 (1932); *Chem. Zentr.*, *I*, 3791 (1937).

(7) W. M. Whaley, M. Meadow, and C. N. Robinson, *J. Org. Chem.*, **19**, 973 (1954).

(8) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 717 (1953).

(9) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 3046 (1952).

(10) G. M. Badger, R. S. Pearce, and R. Pettit, *J. Chem. Soc.*, 3199 (1951).

(11) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940).

(12) A. T. Hawkinson and A. A. Elston, U. S. Patent **2,371,691**.

(13) All melting points were taken in Pyrex capillaries, using a Hershberg melting-point apparatus (Ace Scientific Company) and Anschütz thermometers. The ultraviolet spectra of III and IV were measured in ethanol solution with a Cary Automatic Recording Spectrophotometer, Model 10. The curve of pyrene shown was plotted from Jones' data.[14] Inflection points are indicated by asterisks.

(14) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

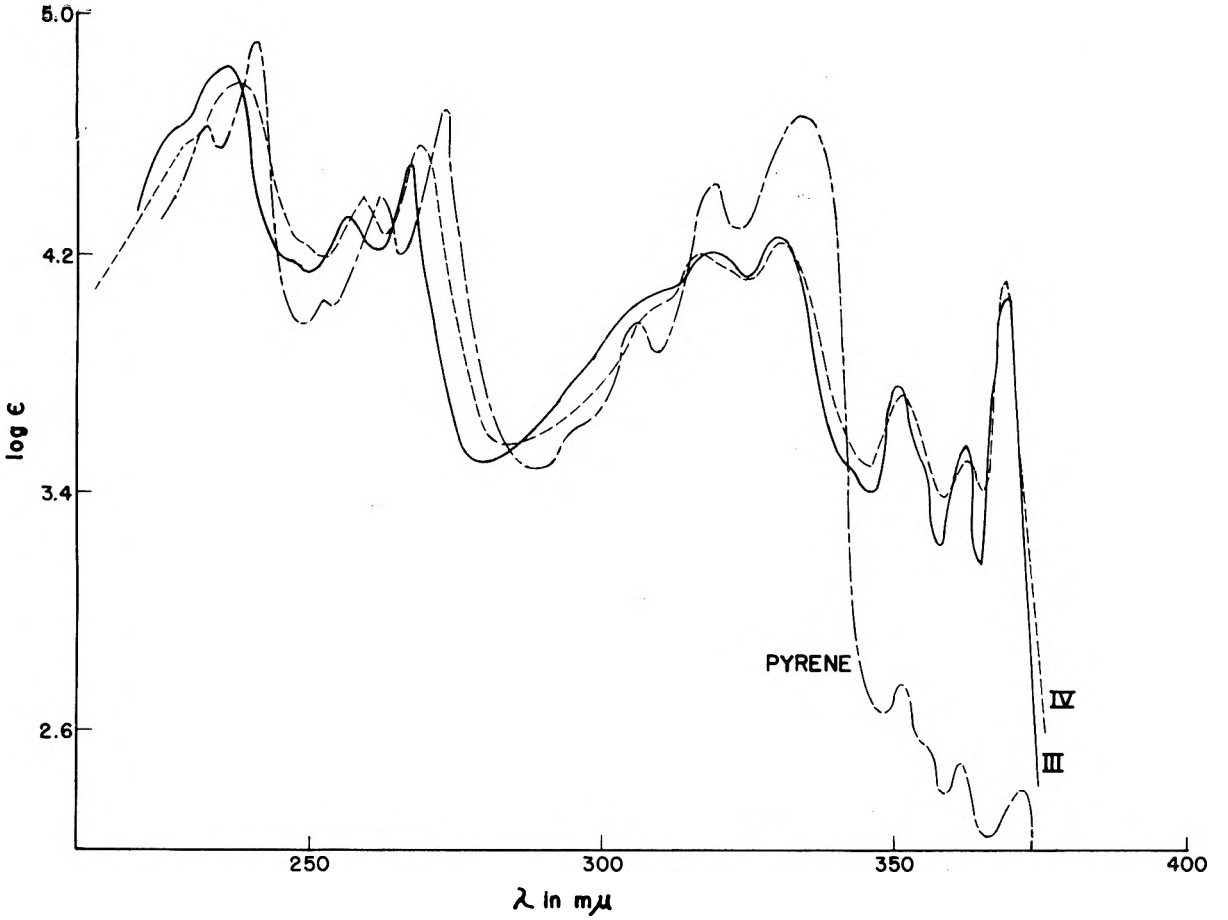


FIG. 1.—ULTRAVIOLET ABSORPTION SPECTRA IN ETHANOL SOLUTION OF: III (——), IV (– – –), AND PYRENE (—·—).

turated with a little methanol. The solid was filtered, washed with methanol and ether and dried, giving 21.5 g. of crude product. Two recrystallizations from benzene gave a product melting at 164.2–165.3° (lit.[15] 161°).

Pyrido[2,3,4,5-lmn]phenanthridine (III). A mixture of 35 g. of anhydrous aluminum chloride and 15 g. of sodium chloride was melted and stirred in an oil bath at 250°. In one lot was added 10.0 g. of 2,2′-diformamidobiphenyl and the mixture was stirred for 2 hr. at 250°, then drowned onto ice and hydrochloric acid. The resulting solution was boiled and filtered from a little insoluble matter.

At this point the solution could be worked up in two ways depending upon whether the hydrochloride (A) or picrate (B) was desired.

(*A*) *Hydrochloride.* The original aqueous hydrolysis mixture was concentrated to incipient crystallization and allowed to cool. The product obtained was recrystallized from a very small volume of water, giving, in about 12% yield, orange needles, m.p. 301–2°.

Anal. Calcd. for $C_{14}H_8N_2 \cdot HCl$; N, 11.62; Cl, 14.75. Found: N, 11.7; Cl, 15.0.

(*B*) *Picrate.* The aqueous hydrolysis mixture was concentrated to a volume of about 300 ml. and was treated with an excess of a methanolic solution of picric acid. The resulting precipitate was filtered, washed with methanol and dried, giving 5.48 g. (30.4% yield) of crude picrate, m.p. 226–8°. It could be recrystallized from methanol in orange-red leaves, m.p. 226.3–228.3°.

Anal. Calcd. for $C_{20}H_{11}N_5O_7$; C, 55.5; H, 2.54; N, 16.2; O, 25.8. Found: C, 54.6, 55.1; H, 3.50, 3.02; N, 16.3, 16.4; O, 25.8.

(*C*) *Base.* The base was obtained by recrystallizing the hydrochloride from pyridine, or by basifying aqueous solutions of the salt and recrystallizing the precipitated base from pyridine. It formed very pale yellow needles, m.p. 220.0–220.7°; $\lambda_{max.}$ 227*, 235, 256, 266.5, 311*, 318, 329, 351.5, 364.5, and 371.8 mμ (log ε 4.61, 4.83, 4.33, 4.50, 4.10, 4.22, 4.27, 3.77, 3.57, and 4.08).

Anal. Calcd. for $C_{14}H_8N_2$: C, 82.4, H, 3.92; N, 13.72. Found, C, 81.9; H, 3.98; N, 14.1.

5,10-Dimethylpyrido[2,3,4,5-lmn]phenanthridine (IV). The same cyclization conditions and isolation technique used to obtain III were applied to II. The crude base was twice recrystallized from pyridine to give a 13% yield of IV, m.p. 260.0–261.4°; $\lambda_{max.}$ 230*, 237, 248*, 258.5, 268, 310*, 316, 320*, 330.5, 352, 364.5, and 371.5 mμ (log ε 4.59, 4.78, 4.25, 4.40, 4.58, 4.05, 4.20, 4.19, 4.27, 3.84, 3.52, and 4.13).

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.7; H, 5.17; N, 12.07. Found: C, 82.7; H, 5.15; N, 12.1.

The *picrate* appeared less stable than that of III; it charred without melting if put into the melting point bath below 260°, but melted instantaneously at 261.0–261.5°.

Acknowledgment. The author is indebted to Mr. H. X. Kaempfen for valuable technical assistance; to Mr. F. C. Dexter for measuring the ultraviolet spectra, and to Mr. O. E. Sundberg and his associates for the microanalyses.

BOUND BROOK, N. J.

(15) Tauber, *Ber.*, **24**, 199 (1891).

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

Application of the Ritter Reaction to Mesityl Oxide and Chalcone

PAUL J. SCHEUER, HENYLSON C. BOTELHO,[1] AND CRELLIN PAULING

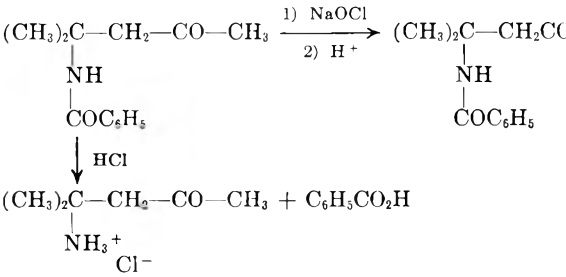
Received November 30, 1956

The acid-catalyzed addition of nitriles to mesityl oxide yields the expected 4-methyl-4-amido-2-pentanones. Chalcone as the olefin component gives rise to only small amounts of the expected adducts in addition to an anomalous product with acetonitrile. The significance of these results is discussed briefly.

An attractive first synthetic step toward the otherwise rather inaccessible 4-oxoperhydrooxindole system seemed to be the acid-catalyzed addition of α-chloroacetonitrile to 2-cyclohexenone according to the general method developed by Ritter.[2] This elegant reaction has since been extended to a variety of systems such as long-chain fatty acids with nitriles[3] or with hydrogen cyanide,[4] olefins with cyanogen chloride,[5,6] haloölefins with nitriles[7,8] and camphene with hydrogen cyanide.[9] Ritter and Hartzel[2d] had successfully utilized several α,β-unsaturated carbonyl compounds such as β,β-dimethylacrylic acid and ethyl cinnamate as the olefin components. However, the results with these systems were less conclusive than with simple olefins as *e.g.*, methyl crotonate or maleic acid failed to react. Furthermore, no report had appeared in the literature of an extension of the Ritter reaction to α,β-unsaturated *ketones* although the Ritter patent[2h] mentions the applicability of the reaction to mesityl oxide. It was therefore felt desirable to study the reaction with some model α,β-unsaturated ketones before proceeding to the cyclohexenone case. This paper deals with the results of these model investigations.

From the standpoint of ready availability and relative dissimilarity mesityl oxide and chalcone were chosen as the model olefin components. Each was reacted with benzonitrile and acetonitrile.

The addition of benzonitrile to mesityl oxide led to the expected 4-methyl-4-benzamido-2-pentanone in yields averaging 50%. The careful experimental directions of Roe and Swern,[3] who in their work with olefinic fatty acids employed an excess of nitrile, were followed initially. But in this case it was found that equimolar quantities of olefin and nitrile led to a more easily purified product. The analytical results and the infrared data (2.91 μ, imine; 5.85 μ, carbonyl; 6.01 μ, amide) were consistent with the structure of the expected adduct. Since this compound had not been reported previously, its structure was confirmed by the following degradative scheme.



The haloform reaction led to β-benzamidoisovaleric acid in 80% yield. The acid was characterized by analytical data, neutral equivalent and comparison of the melting point and that of its anilide with those reported for this acid by Baker and Ollis.[10]

The acid hydrolysis of 4-methyl-4-benzamido-2-pentanone furnished benzoic acid identified by direct comparison, but no diacetone amine or any of its salts. In fact, ammonium chloride was the only other hydrolysis product isolated. This, however, is not too surprising in view of the known decomposition of diacetone amine into ammonia and mesityl oxide,[11] which may have been followed by a reverse aldol reaction leading to acetone. Yet no acetone could be detected at the end of the 30-hr. hydrolysis or after making the solution, from which benzoic acid had been removed, alkaline.

If the acid hydrolysis of this *N-tertiary* benzamide had followed the mechanism suggested for such

(1) In part from the M. S. Thesis of H. C. Botelho, June 1956.

(2) (a) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948); (b) J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048, (1948); (c) F. R. Benson with J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949); (d) L. W. Hartzel with J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949); (e) R. M. Lusskin with J. J. Ritter, *J. Am. Chem. Soc.*, **72**, 5577 (1950); (f) H. Plaut with J. J. Ritter, *J. Am. Chem. Soc.*, **73**, 4076 (1951); (g) J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.*, **74**, 763 (1952); (h) J. J. Ritter, U. S. Patent **2,573,673** (Oct. 30, 1951).

(3) E. T. Roe and D. Swern, *J. Am. Chem. Soc.*, **75**, 5479 (1953).

(4) E. T. Roe and D. Swern, *J. Am. Chem. Soc.*, **77**, 5408 (1955).

(5) F. M. Cowen, *J. Org. Chem.*, **20**, 287 (1955).

(6) E. M. Smolin, *J. Org. Chem.*, **20**, 295 (1955).

(7) Ch. Malen and J. R. Boissier, *Bull. soc. chim. France*, 923 (1956).

(8) R. Maugé, Ch. Malen, and J. R. Boissier, *Bull. soc. chim. France*, 926 (1956).

(9) G. A. Stein, M. Sletzinger, H. Arnold, D. Reinhold, W. Gaines, and K. Pfister, *J. Am. Chem. Soc.*, **78**, 1514 (1956).

(10) W. Baker and W. D. Ollis, *J. Chem. Soc.*, 345 (1949).

(11) E. H. Rodd, ed., *Chemistry of Carbon Compounds*, Elsevier, New York, 1951, Vol. I, pp. 532–5.

substances by Ritter and Minieri,[2a] the primary products should have been benzamide and mesityl oxide. The amide would be expected to react further to yield benzoic acid and the failure to isolate the olefinic ketone can be rationalized by the previous argument. In spite of this failure there seems to be sufficient evidence to consider the structure of the adduct established beyond doubt.

Acetonitrile could also be added to mesityl oxide to yield the exceedingly hygroscopic 4-methyl-4-acetamido-2-pentanone. The yields of this reaction were only about 20% due to some extent to the difficulty of isolating and handling the water-soluble hygroscopic adduct. Its structure was inferred from analytical and infrared data and by analogy with the benzamido compound.

Chalcone proved to be a far less satisfactory olefin component for the Ritter reaction. Benzonitrile did not add at all below 55°. Above that temperature, formation of large amounts of benzamide and tars could not be avoided even when acetic acid was used as a diluent or when phosphoric acid was substituted for sulfuric acid. Small amounts of 3-benzamido-3-phenylpropiophenone could be isolated by extraction of the solid mixture with cyclohexane or by fractional crystallization from ethyl acetate. Analytical and infrared data served to characterize the compound.

Acetonitrile under a wide variety of conditions yielded only small amounts of the expected 3-acetamido-3-phenylpropiophenone, which was characterized by physical methods and by analogy with the mesityl oxide case. This reaction, however, furnished a major crystalline substance which was neutral, contained nitrogen and *sulfur* and formed a crystalline semicarbazone. The outstanding bands in the infrared spectrum of this compound (5.90 μ, benzoyl; 6.00 μ, amide; 7.38 and 8.53 μ, sulfone) point to the possibility that under the conditions of the reaction (4 hr. at 70–80°) sulfonation followed by intramolecular cyclodehydration might have occurred. A reasonable structure for this product might thus be 2-(1′-acetamido-2′-benzoyl)ethylbenzenesulfonic acid sultam. The combustion data agree with a dihydrate of a substance of this composition and an infrared band at 2.85 μ in the spectrum of the mulled solid also indicates a hydrated compound. However, no chemical structure proof has been carried out as yet.[12]

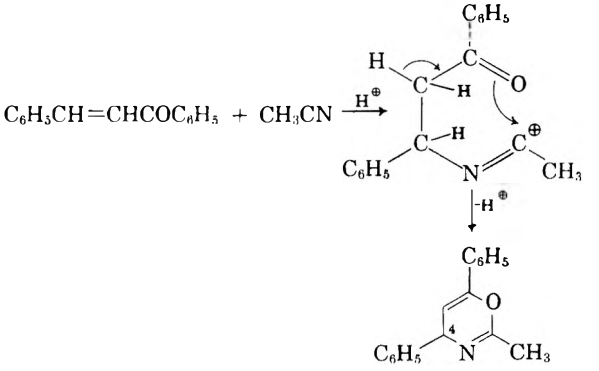
One point emerges readily if one attempts to rationalize these results. Mesityl oxide in contrast to chalcone can provide a favorable tertiary carbonium ion *beta* to the carbonyl to allow attack by the nitrile nitrogen. This would tend to facilitate normal addition at a temperature at which side reactions are negligible. At the higher temperature which is needed for the chalcone reaction polymerization, or at least dimerization,[13] seems to take precedence over attack on the somewhat less favorable secondary carbonium ion. It would be desirable to test this hypothesis by carrying out the reaction with *e.g.* β-methylchalcone. However, it should be noted that Hartzel and Ritter[2d] obtained a 26% yield of the normal adduct from ethyl cinnamate and only 9% from ethyl β-hydroxy-β-methyl-γ-phenylbutyrate, which is structurally equivalent to a compound with a tertiary *beta*-carbon atom. An attempt to answer the further question of the isolation of the sulfur-containing compound from the acetonitrile but not from the benzonitrile reaction should be deferred until the anomalous product has been fully characterized. It may be pointed out, though, that acetonitrile has been proposed as a good solvent in sulfonation reactions.[14]

EXPERIMENTAL[15]

4-Methyl-4-benzamido-2-pentanone. To a solution of 19.6 g. (0.2 mole) of mesityl oxide and 22.0 g. (0.21 mole) of benzonitrile[16] was added 20 ml. of concentrated sulfuric acid. The temperature was kept below 30° by means of an ice bath. After addition was complete the reaction mixture was warmed to 50° and was kept at this temperature for 1 hr. The dark viscous liquid was poured into 300 ml. of ice cold water. The resulting solid was filtered and washed with 10% potassium carbonate solution, then with water. Yield, 20–24 g. (45–55%), m.p. 98–100°. Recrystallization from cyclohexene and dilute ethanol furnished white needles, m.p. 100–101°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.34; H, 7.73; N, 5.29, 5.40.

(12) We are indebted to Dr. J. J. Ritter who, on the basis of unpublished results from his laboratory, pointed out that the anomalous chalcone-acetonitrile adduct might have arisen through cyclization to an oxazine:



Subsequent sulfonation of the 4-phenyl group would lead to a sulfonic acid of empirical composition identical with that of the suggested sultam. The infrared data and the formation of the semicarbazone could equally well be interpreted on the basis of the oxazine. However, the neutral character of our product would require further cyclization of the oxazinesulfonic acid with concomitant loss of the elements of water.

(13) *cf.* H. Wieland, *Ber.* **37,** 1147 (1904).

(14) D. S. Henderson and A. N. Sachanen, U.S. Patent **2,448,370** (Aug. 31, 1948).

(15) (a) All melting points and boiling points are uncorrected. (b) Microanalyses by Drs. Weiler & Strauss, Oxford, England.

(16) A generous gift of benzonitrile from the Tennessee Products and Chemical Corp. is gratefully acknowledged.

2,4-Dinitrophenylhydrazone prepared by Johnson's[17] method and recrystallized from methanol; yellow needles, m.p. 204–205°.

Anal. Calcd. for $C_{19}H_{21}N_5O_5$: C, 57.13; H, 5.30; N, 17.5. Found: C, 57.10; H, 5.20; N, 18.2.

β-Benzamidoisovaleric acid. The haloform reaction with 4-methyl-4-benzamido-2-pentanone was carried out according to *Organic Syntheses*.[18] The resulting acid was recrystallized from water and from dilute ethanol, m.p. 144–146°. (Reported,[10] 141°.).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.32; Neut. equiv., 221. Found: C, 64.55, 64.53; H, 6.89, 6.75; N, 6.15; Neut. equiv. 222 ± 4 (3 determinations in non-aqueous medium[19]).

The anilide of this acid was recrystallized from water and dilute ethanol. White needles, m.p. 172–173°. (Reported,[10] 170°.)

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 73.47, 73.45; H, 6.80, 6.81; N, 9.25.

Hydrolysis of 4-methyl-4-benzamido-2-pentanone. Four g. of the amide was refluxed for 30 hr. with 50 ml. of 12*N* hydrochloric acid. Cooling led directly to the theoretical amount of benzoic acid, as determined by melting point and mixed melting point. The filtrate failed to react with 2,4-dinitrophenylhydrazine reagent. Upon evaporation to dryness it yielded a residue identified as ammonium chloride.

4-Methyl-4-acetamido-2-pentanone. To a solution of 30.0 g. (0.30 mole) of mesityl oxide and 41.0 g. (1.0 mole) of acetonitrile was added dropwise 60 ml. of concentrated sulfuric acid. The temperature was kept below 30° by external cooling. The mixture was then warmed to 70–80° and kept at that temperature for 2 hr. The viscous mixture was poured into 400 ml. of crushed ice and water and stirred vigorously. It was then neutralized with 20% sodium hydroxide solution and extracted with twelve 50-ml. portions of chloroform. The solvent was removed after drying over magnesium sulfate and the residue distilled *in vacuo*. The fraction boiling 140–146°/28 mm. (12.1 g., 25%) was collected and redistilled. The product, b.p. 145–146°/28 mm. crystallized in a vacuum desiccator and was recrystallized from cyclohexane, m.p. 47.5° in an evacuated capillary.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.84; H, 9.50; N, 7.80.

Yellow *2,4-dinitrophenylhydrazone* recrystallized from ethanol, m.p. 194–195°.

Anal. Calcd. for $C_{14}H_{19}N_5O_5$: C, 49.84; H, 5.68; N, 20.8. Found: C, 50.03; H, 5.56; N, 19.8.

3-Benzamido-3-phenylpropiophenone. A solution of 20.8 g. (0.1 mole) of chalcone[20] in 31.2 g. (0.3 mole) benzonitrile was added over 12 min. to 10.4 g. (0.1 mole) of benzonitrile in 33 ml. of concentrated sulfuric acid. The temperature was kept below 80° during the addition and the mixture was stirred for another hour at 70–80°. It was then poured into 400 ml. of crushed ice and water. After standing for 2 hr. the yellow crystalline material was filtered off. Repeated recrystallizations from ethanol and ethyl acetate removed chalcone and benzamide thus leading to a white crystalline solid, m.p. 158–159°.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.88; H, 5.62; N, 4.10.

The orange-yellow *2,4-dinitrophenylhydrazone* was recrystallized from 95% acetone, m.p. 238–239°.

Anal. Calcd. for $C_{28}H_{23}N_5O_5$: C, 66.00; H, 4.55; N, 13.8. Found: C, 65.22; H, 4.81; N, 13.90.

Reaction of chalcone and acetonitrile. To a solution of 20.8 g. (0.1 mole) of chalcone and 16.4 g. (0.4 mole) of acetonitrile was added 34 ml. of concentrated sulfuric acid while the temperature was kept below 30°. The mixture was then heated to 70–80° for 4 hr. and poured into 300 ml. of ice water. The solids which precipitated immediately were filtered and washed with small portions of chloroform to remove the yellow chalcone. Recrystallization from isopropyl alcohol and dilute ethanol led to a white solid, m.p. 221° (dec.). The substance was neutral and contained nitrogen and sulfur.

Anal. Calcd. for $C_{17}H_{15}NO_4S \cdot 2H_2O$: C, 55.89; H, 5.24; S, 8.77. Found: C, 56.31; H, 5.70; S, 8.70.

The substance formed a colorless semicarbazone which melted at 251–252° after recrystallization from methanol and isopropyl alcohol.

By recrystallizing the chloroform-washed material from dimethylformamide, followed by repeated recrystallizations from water and from dilute ethanol, an analytical sample of the normal adduct, 3-acetamido-3-phenylpropiophenone, m.p. 104–105°, could be obtained.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.41; H, 6.69; N, 4.97.

It formed a yellow *2,4-dinitrophenylhydrazone*, m.p. 211°, after recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{21}N_5O_5$: C, 61.74; H, 4.73; N, 15.6. Found: C, 61.53; H, 4.48; N, 15.2.

Acknowledgment. It is a pleasure to acknowledge the assistance of Dr. C. Djerassi and Dr. R. H. Eastman with the determination of most of the infrared spectra and, particularly, the generous financial support of this work by a grant from Research Corporation.

HONOLULU 14, HAWAII

(17) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951).

(18) *Org. Syntheses*, Coll. Vol 2, 428 (1943).

(19) J. S. Fritz, *Acid-Base Titrations in Non-Aqueous Solvents*, The G. Frederick Smith Chemical Co., Columbus, O., 1952, pp. 28–29.

(20) *Org. Syntheses*, Coll. Vol. 1, 2nd Edition, 78 (1941).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WESTINGHOUSE RESEARCH LABORATORIES]

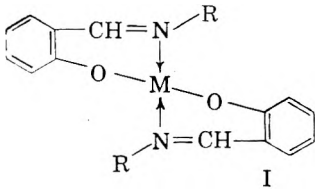
Copper (II) and Nickel (II) *N*-(*n*-alkyl)salicylaldimine Chelates

ROBERT G. CHARLES

Received November 8, 1956

A number of copper and nickel salicylaldimine chelates derived from straight chain primary amines have been prepared. Melting point *vs.* chain length plots are presented and comparisons made between the two series of compounds. Copper and nickel chelates of this type are suggested as suitable derivatives for characterizing primary amines. Nickel chelates of the type studied are characteristically higher melting than are the corresponding copper compounds.

A number of chelates of the general type I have been reported in the literature.[1] Of the compounds I where R is a simple straight chain hydrocarbon



M = Cu or Ni

I

group, however, only the parent methyl compounds appear to have been prepared.[2,3] This paper describes the preparation of two series of chelates I where R is varied from methyl to *n*-tetradecyl. These compounds have been prepared by adaptations of conventional methods[2] involving first the condensation of salicylaldehyde with the appropriate primary amine (RNH_2), followed by reaction with a copper or nickel salt in the presence of a base. The compounds are obtained in good yields and are readily purified by recrystallization.

All the chelates obtained are strongly colored green or brown solids. Except for the highest members of the series, all are beautifully crystalline. All the compounds studied are moderately soluble in organic solvents and insoluble in water. It was observed that, in methyl alcohol, the copper chelates are appreciably more soluble than are the corresponding nickel chelates.

The compositions and properties of the copper chelates are listed in Table I and of the nickel chelates in Table II. In every case the compound corresponds in composition to unsolvated I. Molecular weights of several of the copper and nickel chelates were determined in freezing dioxane. All of the compounds were found to be monomeric in this solvent.

In Figure 1 the melting points of the copper and nickel chelates are plotted as a function of chain length for R. The curves obtained for the two series of chelates are very similar in appearance. In each curve a rise in melting point occurs from butyl to amyl and from decyl to dodecyl. Otherwise the melting point decreases with increasing chain length for both series. In each case the melting point of the nickel chelate is higher than that of the corresponding copper chelate. This fact suggests that intermolecular forces are characteristically greater for nickel chelates of this type than for the analogous copper compounds. This conclusion is also in agreement with the greater solubilities found for the copper chelates in methanol.

TABLE I

COPPER CHELATES OF *N*-(*n*-ALKYL)SALICYLALDIMINE CHELATES (I, M = CU)

R	Prep. Procedure	M.P., °C	% Copper Calcd.	% Copper Found	Appearance
Methyl	A	158.5–159.0[a]	19.15	19.13	Green needles
Ethyl[b]	A	151.7–151.9	17.65	17.65	Dark green plates
n-Propyl	A	123.0–123.6	16.38	16.30	Short dark green needles
n-Butyl[c]	B	80.5– 81.0	15.27	15.20	Dark green plates
n-Amyl[d]	C	96.2– 96.8	14.28	14.14	Brown-green needles
n-Hexyl	C	83.8– 84.4	13.46	13.52	Dark green plates
n-Heptyl	C	80.0– 80.5	12.70	12.61	Brown-green needles
n-Octyl[e]	C	66.0– 66.4	12.03	12.14	Brown plates
n-Decyl	C	61.2– 62.0	10.87	10.78	Light brown plates
n-Dodecyl[f]	C	67.3– 67.6	9.92	9.94	Short brown needles
n-Tetradecyl	C	56.5– 58.0	9.12	9.13	Greenish brown microcrystalline powder

[a] Reported: 158°.[2] [b] % N: Calcd. 7.79; Found 7.58. [c] Molecular weight: Calcd. 416.0; Found 423. [d] Molecular weight: Calcd. 445.1; Found 419. % N: Calcd. 6.32; Found 6.30. [e] Molecular weight: Calcd. 528.2; Found 524. [f] % N: Calcd. 4.35; Found 4.34.

(1) A. Martell and M. Calvin, *Chemistry of the Metal Chelates Compounds*, Prentice-Hall, Inc., New York, 1952.

(2) P. Pfeiffer and H. Glaser, *J. prakt. Chem.*, **153**, 270 (1939).

(3) V. Klemm and K. Raddatz, *Z. anorg. u. allgem. Chem.*, **250**, 207 (1942).

TABLE II

NICKEL CHELATES OF *N*-(*n*-ALKYL)SALICYLALDIMINE CHELATES (I, M = Ni)

R	Prep. Procedure	M.P., °C	% Nickel Calcd.	% Nickel Found	Appearance
Methyl	A	206.2–207.2	17.95	17.96	Mixture of green needles and plates[a]
Ethyl	B	177.2–177.6	16.53	16.33	Very dark green plates
n-Propyl[b]	A	164.8–165.6	15.32	14.80	Very dark green plates
n-Butyl[c]	B	141.8–142.4	14.27	14.03	Brownish green plates
n-Amyl[d]	C	146.7–147.5	13.36	13.20	Fine green needles
n-Hexyl	B	122.3–123.4	12.56	12.46	Green needles
n-Heptyl	C	121.4–121.6	11.85	11.90	Fine green needles
n-Octyl[e]	C	100.5–101.0	11.21	11.13	Brown needles
n-Decyl	C	89.4– 90.7	10.13	10.17	Small green plates
n-Dodecyl[f]	C	98.6– 98.8	9.23	9.42	Green microcrystalline powder
n-Tetradecyl	C	87.0– 88.5	8.49	8.57	Green microcrystalline powder

[a] This was the only compound studied which appears to exist in more than one crystalline form. [b] % N: Calcd. 7.32; Found 7.28. [c] Molecular weight: Calcd. 411.2; Found 417. [d] Molecular weight: Calcd. 440.2; Found 473. % N: Caled. 6.38; Found 6.27. [e] Molecular weight: Calcd. 523.4; Found 567. [f] % N: Calcd. 4.41; Found 4.21.

The ease of preparation and purification of the salicylaldimine chelates, together with their sharp and convenient melting points, suggest the use of these compounds for the characterization of primary amines.[4] In the case of those amines whose chelate derivatives have similar melting points, identification is still possible, by means of mixed melting points. Melting points were determined on mixtures of several pairs of compounds from both the copper and nickel series. In all cases definite melting point depressions were observed.

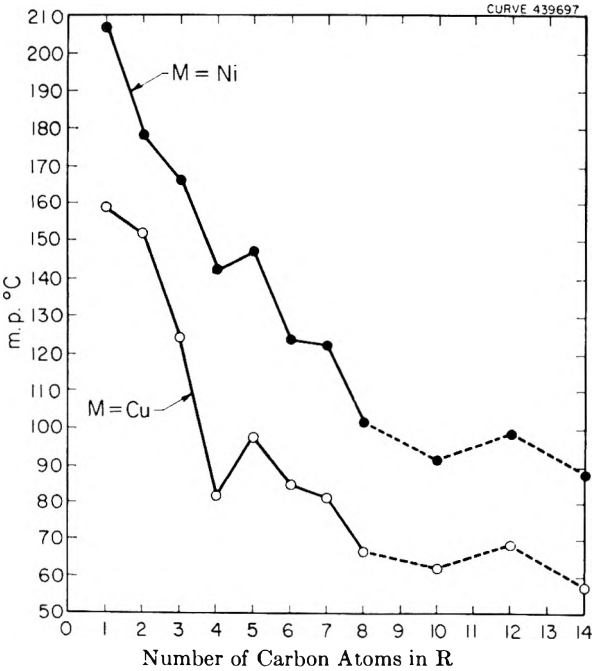
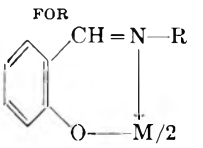


FIG. 1.—MELTING POINT AS A FUNCTION OF CHAIN LENGTH FOR



EXPERIMENTAL

Preparation of compounds. The chelates were prepared by adaptations of existing methods.[2] One of the three methods below was used in each case as indicated in Tables I and II. The initially formed Schiff base compounds were not isolated but were reacted directly in solution, with the metal salt, to form the Schiff base chelates.

Method A. To 6.1 g. (0.05 mole) of salicylaldehyde dissolved in 100 ml. of methyl alcohol was added 0.1 mole (2 fold excess) of the primary amine (either as the pure compound or as a 25% solution in water) and the mixture allowed to stand a few minutes at room temperature. A solution of 0.025 mole of copper or nickel acetate in 100 ml. of distilled water was added followed by a solution of 5 g. of sodium acetate trihydrate in 50 ml. of water. The mixture was heated nearly to boiling and stirred for 15 to 30 min. The mixture was allowed to stand at room temperature for 1 hr., or overnight, and the solid chelate filtered off on a Buchner funnel. The compound was air dried and recrystallized from methanol. The recrystallized compound was dried at room temperature *in vacuo* over $CaCl_2$. One recrystallization gave an analytically pure product in all cases. Yields of the unrecrystallized products were generally above 90%.

Method B. The procedure differed from Method A only in that a solution of 2 g. of sodium hydroxide in 50 ml. of water was added following the sodium acetate solution.

Method C. The procedure differed from Method B only in that 0.05 mole of the amine (as the pure compound) was used rather than a two fold excess, as in Method A and B.

Melting Points. Melting points were determined in open-end capillaries using a Hershberg apparatus and short range Anschütz thermometers (uncalibrated). Values reported in Tables I and II were determined by preheating the bath to 10° C. below the melting point before introducing the capillary. In most cases preheating the bath was unimportant. In the case of bis(*N*-methylsalicylaldimine) nickel (II), however, the compound decomposed on slow heating to an infusible product before the normal melting point was reached.

(4) For this purpose it is necessary to insure a small excess of the amine during the preparation of the chelate to prevent the possible coprecipitation of the copper or nickel chelate of salicylaldehyde. A large excess of amine is not harmful for the lower amines but tends to contaminate the product for the higher ones.

The melting points of the chelates studied were found not to change appreciably after storage of the compounds at room temperature for a period of 1 year.

Mixed melting points were determined for the following pairs of compounds after grinding approximately equal quantities together in a small mortar. Values obtained: Copper chelates: methyl-ethyl, 97–100°; heptyl-octyl, 56–61°; decyl-dodecyl, 46–50°; dodecyl-tetradecyl, 45–49°. Nickel chelates: heptyl-octyl, 95–96°; decyl-dodecyl, 72–75°; dodecyl-tetradecyl, 71–74°.

Molecular Weights. The molecular weights of the chelates were determined cryoscopically in 1,4-dioxane using weighed quantities of the solute and solvent and using a thermometer which could be estimated to ±0.01C°. The concentration of the solutions was about 0.1*M*. The apparatus used was capable of an accuracy of about ±5% in the M.W. The dioxane used was refluxed over sodium and distilled through an efficient fractionating column. A value of 4.63 was used for K_f.

Analyses. The organic portions of the compounds were destroyed by repeatedly evaporating with mixtures of hydrochloric, nitric, and sulfuric acids. Copper was determined in the residues gravimetrically with 8-hydroxyquinoline, and nickel gravimetrically with dimethylglyoxime. Nitrogen was determined by the Kjeldahl method using separate samples.

Acknowledgments. The writer is indebted to Miss Dorothy L. Anderson and Mr. Robert Berberich for invaluable technical assistance and to Miss M. I. Mistrik and Mr. J. F. Reed for certain of the analyses.

PITTSBURGH 35, PA.

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Preparation of *N,N′*-Bis(α-haloacyl)hydrazines[1]

ALFRED KREUTZBERGER

Received September 18, 1956

The preparation of several *N,N′*-bis(α-haloacyl)hydrazines from hydrazine hydrate and α-haloacid halides or α,α′-dihaloacid anhydrides respectively is described.

The well known benzidine rearrangement of hydrazo compounds proceeding under the influence of acids sometimes fails, *e.g.*, with hydrazothiazoles-(2,2′).[2] However, in this case, it was found possible to bring about the benzidine rearrangement by means of phthalic anhydride.[3] In order to test the scope of the applicability of the phthalic anhydride reaction on isomeric hydrazothiazoles, an effort was made to synthesize hydrazothiazole-(4,4′) and -(5,5′). Interaction of 2,4-dimethyl-5-bromothiazole[4] with hydrazine hydrate in a sealed tube gave only decomposition products. Thiazolinones, such as 2-phenylthiazolinone-(4),[5] do not react with hydrazine hydrate. The *N,N′*-bis(α-haloacyl)hydrazines (II) and thioamides either did not react or formed the ammonium halides as decomposition products. Although synthesis of the hydrazothiazoles-(4,4′) or -(5,5′) was not achieved, preparation of some α-haloacylhydrazines is described here since examples of this class of substances do not appear to have been recorded previously in the literature.

Although the reaction of acid chlorides (III) with hydrazine hydrate is a standard procedure for preparing *N,N′*-diacyl-hydrazines (IV),[6] no literature references are to be found dealing with the application of this reaction utilizing the simpler acid chlorides, *e.g.* III, R = CH_3, $C_6H_5CH_2$, C_2H_5, or C_3H_7. Consequently, *N,N′*-diphenacetylhydrazine (IV, R = $C_6H_5CH_2$) was prepared from phenacetyl chloride (III, R = $C_6H_5CH_2$) and hydrazine hydrate. These components reacted vigorously to give a 28% yield of IV (R = $C_6H_5CH_2$), a compound hitherto accessible only through protracted procedures.[7]

In a similar manner the preparation of II was accomplished by the reaction of α-haloacid halides (I) with hydrazine hydrate.[8] The investigation of the end products of this reaction indicated the formation of considerable amounts of the corresponding α-haloacids with lesser amounts of II. Better yields of II were obtained by using inert solvents such as

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, Baltimore, Md.

(2) D. Markees, M. Kellerhals, and H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 304 (1947); H. Beyer, H. Schulte, and G. Henseke, *Chem. Ber.*, **82**, 143 (1949).

(3) H. Beyer and A. Kreutzberger, *Chem. Ber.*, **84**, 518 (1951).

(4) G. M. Dyson and R. F. Hunter, *J. Indian Chem. Soc.*, **8**, 147 (1931).

(5) P. Chabrier and S. Renard, *Compt. rend.*, **226**, 582 (1948).

(6) H. Wieland, *Die Hydrazine*, Verlag Ferdinand Enke, Stuttgart (1913).

(7) A. Pinner and Göbel, *Ber.*, **30**, 1889 (1897); T. Curtius and E. Boetzelen, *J. prakt. Chem.*, [2] **64**, 318 (1901); G. Klein and W. Fuchs, *Biochem. Z.*, **213**, 49 (1929).

(8) Hydrazine hydrate has been found to effect reductive dehalogenation of some halogenocompounds [see *e.g.* B. W. Howk and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 3372 (1933)]. Consequently, anhydrous hydrazine was not used by the author since it is known to be an even stronger reducing agent than hydrazine hydrate [see *e.g.*, S. Dutt and K. Sen, *J. Chem. Soc.*, 3420 (1923); 2971 (1925)].

TABLE I

N,N'-BIS(α-HALOACYL)HYDRAZINES

$$\begin{matrix} Hal & O & & O & Hal \\ | & \| & & \| & | \\ R{-}CH{-}C{-}N & - & N{-}C{-}CH{-}R \end{matrix} \qquad (II)$$

Starting Material	Most Suitable Diluent	End Product	Yield, %	Recrystallized from	M.P., °C. (Corr.)	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Hal Calcd.	Hal Found
I, R = H Hal = Cl	Chloroform	II, R = H Hal = Cl (IIa)	21.7	Ethyl acetate	172–173	25.97	26.17	3.27	3.50	15.15	14.91	Cl 38.33	Cl 37.98
I, R = CH_3[11] Hal = Br	Ethyl acetate	II, R = CH_3 Hal = Br (IIb)	19.2	Ethyl acetate	221–222	23.86	23.99	3.34	3.36	9.28	9.03	Br 52.93	Br 53.25
I, R = C_2H_5[11] Hal = Br	Ethyl acetate	II, R = C_2H_5 Hal = Br (IIc)	27.7	Methanol-water 3:1	240					8.49	8.68	Br 48.44	Br 48.38
I, R = C_6H_5[12] Hal = Cl	Ethyl acetate	II, R = C_6H_5 Hal = Cl (IId)	48.5	Acetone-water 3:2	227–228					8.31	8.39	Cl 21.03	Cl 21.24

ether, chloroform, benzene, dioxane, or ethyl acetate. In particular, use of ethyl acetate turned out to be very advantageous, since at room temperature it will dissolve large amounts of α-haloacids but practically no II. Separation of II is therefore easily accomplished. Because of the much greater reactivity of the α-haloacid halides compared to ethyl acetate used as solvent, the latter will not react with hydrazine hydrate under the conditions employed. Furthermore, to avoid the possible formation of long-chained molecules by the concurrent reaction of the α-halogen in I, it was expedient in this reaction to have I always present in excess, a condition that was also used in the interaction of higher molecular diamines with haloacid halides.[9] The stoichiometric ratio of 1 mole of hydrazine hydrate to 2 moles of I turned out to be the most favorable one. The compounds (II) prepared in this way are compiled in Table I.[10] They are soluble in all common organic solvents upon boiling except ether, petroleum ether, and carbon disulfide. In hot water, IIa is easily soluble, IIb slightly soluble, and IIc and IId are insoluble.

The yield of II could be improved considerably in those cases where the anhydrides of the α-haloacids corresponding to I were known. The results obtained from the reaction of α,α'-dihaloacid anhydrides (V) with hydrazine hydrate are given in Table II.

TABLE II

N,N'-BIS(α-HALOACYL)HYDRAZINES FROM α,α'-DIHALOACID ANHYDRIDES

Starting Material	End Product	Yield in %
V, R = H Hal = Cl	IIa	49.6
V, R = CH_3[13] Hal = Br	IIb	44.6
V, R = C_2H_5[13] Hal = Br	IIc	55.6

EXPERIMENTAL

N,N'-Diphenacetylhydrazine (IV) (R = $C_6H_5CH_2$). To 30 g. of phenylacetyl chloride stirred and cooled with ice were added slowly 5 g. of hydrazine hydrate. A vigorous reaction occurred, and a white material precipitated. The latter, after standing overnight, was vacuum-filtered, dissolved in

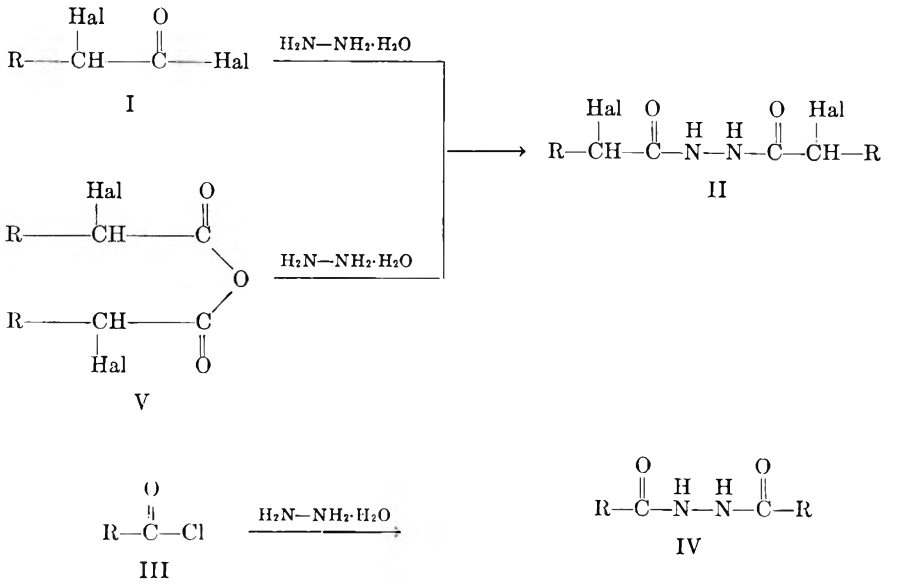
(9) T. v. Braun, F. Dengel, and A. Jacob, *Ber.*, **70**, 994 (1937).

(10) While this work was in progress, a patent [P. Schlack, German Patent No. 819,405 (to Kunstseidefabrik Bobingen, Germany) October 31, 1951; *Chem. Abstr.*, **47**, 2202 (1953)] was published describing IIa as obtained by a different route, namely, from α-chloroacetic anhydride and carbazic acid. By contrast the synthesis described in this paper does not necessitate conversion of hydrazine hydrate into carbazic acid. The identity of IIa obtained by the patented procedure given with the product obtained by the process described in this paper was confirmed by mixed melting point.

(11) T. Volhard, *Ann.*, **242**, 161 (1887).

(12) C. Bischoff and P. Walden, *Ann.*, **279**, 122 (1894).

(13) C. Bischoff and P. Walden, *Ber.*, **27**, 2949 (1894).



25 ml. of hot pyridine, and, while still hot, water was added until crystallization started. Thus, 7.3 g. (28.2%) of well-shaped leaflets were obtained, melting at 243°. No depression in melting point occurred when mixed with an authentic sample.[7]

As an example for the formation of II from I: *N,N'-Bis(α-chlorophenylacetyl)hydrazine* (*IId*). An amount of 8.3 g. of hydrazine hydrate was added dropwise to a well stirred and ice cooled solution of 63 g. of phenylchloroacetyl chloride (I, R = C_6H_5, Hal = Cl) in 200 ml. of ethyl acetate, thereby precipitating a white material. The reaction contents were heated for 1.5 hours on the steam bath, filtered hot, and the filter cake extracted several times with 300 ml. portions of ethyl acetate. The ethyl acetate extracts, upon cooling, furnished 27.2 g. (48.5%) of a microcrystalline white substance (IId), which, upon recrystallization from acetone-water (3:2), was obtained as white needles, melting at 227–228°.

As an example for the preparation of II from V: *N,N'-Bis(α-bromobutyryl)hydrazine* (*IIc*). To an ice cooled solution of 63.2 g. of α-bromobutyric anhydride (V, R = C_2H_5, Hal = Br) in 300 ml. of absolute ether 5 g. of hydrazine hydrate was added dropwise with stirring, thereby forming a white precipitate. When the hydrazine hydrate had been added, the reaction mixture was heated for 2 hr. on the steam bath to gentle boiling and then filtered hot. The filter cake was repeatedly digested with 500 ml. of ethyl acetate. From the ethyl acetate extracts, upon cooling, a total yield of 18.4 g. (55.6%) of white needles was obtained. After recrystallization from a methanol-water mixture (3:1), the needles melted at 240°.

Acknowledgment. The author is very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

COLUMBUS, OHIO.

Notes

A department for short papers of immediate interest.

4-(*p*-Dimethylaminostyryl)quinolines[1]

CARL TABB BAHNER, CLARENCE COOK, JOHN DALE, JOHN FAIN, EDGAR FRANKLIN, J. C. GOAN, WILLIAM STUMP, AND JOAN WILSON

Received November 26, 1956

Recent observations at the Medical Division of the Oak Ridge Institute of Nuclear Studies[2,3] and the Wistar Institute of Anatomy and Biology[4,5] of the effects of 4-(*p*-dimethylaminostyryl)quinoline (I)[6,7] on tumors have encouraged the preparation of other similar compounds. A systematic study of the effects of small variations in structure upon the antitumor activity and toxicity of such compounds, similar to the studies of Browning, Cohen, Ellingworth, and Gulbransen[8] on trypanocidal styrylquinoline salts and the study of Haddow, Harris, Kon, and Roe[9] on the stilbenes, is being undertaken.

The compounds listed in Table 1 have been synthesized according to plan to include at least one example of substitution of each possible position on the quinoline ring by a methyl or benzo-group.

TABLE I

4-(*p*-DIMETHYLAMINOSTYRYL)QUINOLINE

Position of Substitution	Yield, %	M.P., °C. (corr.)	Analyses[a] Calcd. C	Calcd. H	Found C	Found H
3-Methyl	55	166	83.29	6.99	83.40, 83.26	7.13, 6.95
6-Methyl	20	157			83.21, 83.07	7.05, 6.86
7(or 5)-Methyl	43	153			83.26, 83.33	7.10, 7.08
8-Methyl	44	154[b]			83.40, 83.30	7.07, 6.98
3,6-Dimethyl	10	98	83.40	7.33	83.77, 83.66	7.28, 7.43
3,8-Dimethyl	18	146			83.35, 83.50	7.28, 7.29
5,7-Dimethyl	45	172			83.29, 83.53	7.40, 7.48
5,8-Dimethyl	15	159			83.77, 83.51	7.29, 7.21
6,7(or 5,6)-Dimethyl[c]		226			83.59, 83.35	7.29, 7.20
6,8-Dimethyl		145			83.26, 83.27	7.30, 7.28
7,8-Dimethyl	21	153			83.52, 83.38	7.23, 7.48
2,3-Benzo[d]	20	256	85.15	6.21	85.48, 85.53	6.34, 6.56
5,6-Benzo	69	163			85.25, 85.37	6.23, 6.10
7,8-Benzo[d,e]	27	184				
6-Iodo	35	205	57.01	4.28	56.83, 56.91	4.38, 4.39
6-Bromo	41	178	64.60	4.85	64.53, 64.52	5.09, 4.89
6-Chloro	47	165	73.90	5.55	73.86, 73.86	5.49, 5.53
7(or 5)-Chloro	40	145			74.04, 73.95	5.61, 5.59
8-Chloro	46	196			74.04, 74.05	5.74, 5.71

[a] Carbon and hydrogen analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn. [b] A sample prepared by heating *p*-dimethylaminobenzaldehyde with 8-methyllepidine in the presence of a smaller amount of zinc chloride 6 hr. at 180–200° melted at 196.5–198°. *Anal.* Found: C, 83.24, 83.46; H, 6.79, 6.79. The difference between the two samples is being investigated further. [c] The 5,6-dimethyl structure for this compound seems much less probable. [d] Prepared by the method of Clapp and Tipson. [e] R. J. Gobeil and C. S. Hamilton, *J. Am. Chem. Soc.*, **67**, 511 (1945).

Since halogen atoms differ from methyl groups in their effects upon the electrical forces in and around the molecule, a number of halogen-substituted compounds have been included. A further reason for including the benzoquinoline compounds is the fact that I and its methiodide have been found to be more active against Lymphoma 8 than are

(1) This research was supported by grants from the American Cancer Society, the Research Corporation and the Medical Research Foundation. The Cancer Chemotherapy National Service Center supplied *p*-dimethylaminobenzaldehyde.

(2) C. T. Bahner, *Cancer Research*, **15**, 588 (1955).

(3) C. T. Bahner, *Cancer Research Supplement No. 4.*

(4) M. R. Lewis, B. Hughes, C. T. Bahner, and Bates, *Growth*, **19**, 1 (1955).

(5) M. R. Lewis, B. Hughes, and Bates, *Growth*, **19**, 323 (1955).

(6) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(7) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

(8) C. H. Browning, J. B. Cohen, S. Ellingworth, and H. Gulbransen, *Proc. Royal Soc., B.*, **100**, 293 (1926); C. H. Browning, J. B. Cohen, S. Ellingworth, and H. Gulbransen, *Proc. Royal Soc., B.*, **105**, 99 (1929).

(9) A. Haddow, R. J. C. Harris, G. A. R. Kon, and E. M. I. Roe, *Phil. Trans. Royal Soc. London*, **241**, 147 (1948).

the corresponding pyridine compounds. It might be that the third ring of the benzoquinolines would make them even more active. Haddow, Harris, Kon, and Roe[9] reported that 5-(*p*-dimethylaminostyryl)acridine, which may be thought of as 4-(*p*-dimethylaminostyryl)-2,3-benzoquinoline, had a slight but significant inhibitory effect on the growth of Walker 256 tumor in rats. When we attempted the synthesis of this compound, we obtained a product having the correct composition, but melting at 256° instead of 237–239°, the melting point reported by Porai-Koschitz[10] for his product.

All three benzoquinolines and most of the other compounds listed appeared active when tested against Lymphoma 8. There was a wide range, however, between 4-(*p*-dimethylaminostyryl)-3-methylquinoline and the relatively inactive 4-(*p*-dimethylaminostyryl)-6-iodoquinoline. Details of these tests, carried out at the Wistar Institute of Anatomy and Biology through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey Bates, and with the financial assistance of a grant from the National Cancer Institute, are to be reported elsewhere.

EXPERIMENTAL

The substituted lepidines used were prepared by reaction of substituted anilines with methyl vinyl ketone by the method of Campbell and Schaffner.[11] Methyl isopropenyl ketone furnished by the Celanese Corporation of America was used in place of methyl vinyl ketone to obtain lepidines containing a 3-methyl group.

The following method of preparing the styrylquinolines produced substantially improved yields with less inconvenience than the method we had used previously. Anhydrous zinc chloride, the lepidine, and *p*-dimethylaminobenzaldehyde were mixed in the proportion of 1 mole:2 moles:4 moles and heated 16 to 24 hr. at 110–120°. Water vapor was permitted to escape and the mixture was stirred at intervals. Chloroform, about 4 ml. per gram of starting materials, was added cautiously to the hot mass and boiled under a reflux condenser. The undissolved zinc salt was recovered by filtration, washed with more chloroform or ether, and dried. This dark red solid was triturated with excess 8*N* ammonium hydroxide and allowed to stand 1 hr. The yellow styrylquinoline liberated was washed with water and recrystallized from methanol, isopropanol, or ethyl acetate. Commercial methylpentanes were used in a Soxhlet extractor to separate the product from zinc salts and other insoluble impurities. An additional quantity of product was recovered from the chloroform solution by washing it with 8*N* sodium hydroxide until basic, then with water, drying over sodium sulfate, distilling off the solvent and excess aldehyde under vacuum, and recrystallizing the residue. The 3-methyl compounds were recovered solely from the chloroform solution, since they did not form insoluble zinc salts under the conditions employed.

DEPARTMENT OF CHEMISTRY
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

(10) A. Porai-Koschitz, *Centr.*, *II*, 1528 (1907).

(11) K. N. Campbell and I. J. Schaffner, *J. Am. Chem. Soc.*, **67**, 86 (1945).

Isoquinoline Analogs of 4-(*p*-Dimethylaminostyryl)quinoline[1]

CARL TABB BAHNER, JOAN WILSON, MARY WEST, GEORGE BROWDER, J. C. GOAN, CLARENCE COOK, JOHN FAIN, EDGAR FRANKLIN, AND ALBERT MYERS

Received November 26, 1956

Studies[2,3] at the Wistar Institute of Anatomy and Biology and the Oak Ridge Institute of Nuclear Studies have shown that 4-(*p*-dimethylaminostyryl)quinoline (Ia)[4,5] and its methiodide (Ib)[6] administered in the diet of rats bearing Lymphoma 8 tumors brought about regression of the tumors, and that a number of related compounds showed different potencies in this respect. In order to learn the significance of structural relations, isoquinoline isomers of Ia and Ib, and other closely related isoquinoline derivatives were prepared for testing.

4-(*p*-Dimethylaminostyryl)quinazoline (III) III combines structural features of Ia and IIa. Siegle and Christensen[7] were unable to isolate any 4-styrylquinazoline from the tar obtained by reaction of benzaldehyde with 4-methylquinazoline, but III was prepared readily by the method described below.

It has been reported that Ia was more effective than the corresponding 2-(*p*-dimethylaminostyryl)-quinoline compound, Ic, and Ib was more active than Id. The isoquinoline compound IIa resembles Ia in having the styryl group attached to the heterocyclic ring at a position adjacent to the benzene ring, but resembles Ic in having the styryl group attached to a carbon atom adjacent to the ring nitrogen. On the other hand IIc resembles Ic both in the fact the styryl group is attached to a carbon farther from the benzene ring and the fact that the styryl group is attached to a carbon adjacent to the ring nitrogen. Observations at the Wistar Institute of Anatomy and Biology,[8] to be

(1) The organic syntheses reported here were supported in part by grants from the American Cancer Society, the Medical Research Foundation, and a Frederick Gardner Cottrell Grant from the Research Corporation to Carson-Newman College.

(2) B. Hughes, A. L. Bates, C. T. Bahner, and M. R. Lewis, *Proc. Soc. Exptl. Biol. Med.*, **88**, 230 (1955); M. R. Lewis, B. Hughes, C. T. Bahner, and A. L. Bates, *Growth*, **19**, 1 (1955); M. R. Lewis, B. Hughes, and A. L. Bates, *Growth*, **19**, 323 (1955).

(3) C. T. Bahner, *Cancer Research*, **15**, 588 (1955).

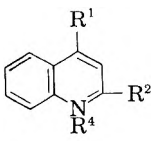
(4) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(5) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

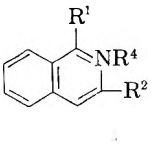
(6) C. T. Bahner, E. S. Pace, and R. Prevost, *J. Am. Chem. Soc.*, **73**, 3407 (1951).

(7) J. Siegle and B. E. Christensen, *J. Am. Chem. Soc.*, **73**, 5777 (1951).

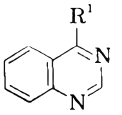
(8) These observations were made possible through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey Bates, and a grant from the National Cancer Institute.



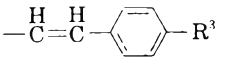
I



II



III



Y

	R^1	R^2	R^3	R^4
Ia	Y	H	$(CH_3)_2N$—	none
Ib	Y	H	$(CH_3)_2N$—	CH_3I
Ic	H	Y	$(CH_3)_2N$—	none
Id	H	Y	$(CH_3)_2N$—	CH_3I
IIa	Y	H	$(CH_3)_2N$—	none
IIb	Y	H	$(CH_3)_2N$—	CH_3I
IIc	H	Y	$(CH_3)_2N$—	none
IId	H	Y	$(CH_3)_2N$—	CH_3I
IIe	Y	H	$(CH_3CH_2)_2N$—	none
IIf	Y	H	$O(CH_2CH_2)_2N$—	none
III	Y	H	$(CH_3)_2N$—	none

published in detail elsewhere, indicated that the IIa, IIc, IIe and III were all less active than Ia against Lymphoma 8. The methiodides were less active than the corresponding free bases. The presence of the morpholino group, in IIf, in place of the dialkylamino group, reduced toxicity and activity against Lymphoma 8.

EXPERIMENTAL

3-(*p*-Dimethylaminostyryl)isoquinoline (IIc) was obtained readily from its methiodide (IId) by the method of Erlenmeyer, Baumann, and Sorkin[9] although 1-(*p*-dimethylaminostyryl)isoquinoline (IIa) was not so readily obtained from its methiodide (IIb), and 4-(*p*-diethylaminostyryl)-quinoline methiodide (Ib) decomposed to yield an unidentified liquid resembling lepidine in odor.

1-(p-Dimethylaminostyryl)isoquinoline (IIa). A mixture containing 15 g. (0.105 mole) of 1-methylisoquinoline purchased from Sapon Laboratories, 135 g. (0.90 mole) of *p*-dimethylaminobenzaldehyde and 5.3 g. (0.039 mole) of zinc chloride was heated 6 hr. at 200°, cooled somewhat and dissolved in 250 ml. of chloroform. The solution was washed with 150 ml. of 8*N* sodium hydroxide, then with water, and dried over sodium sulfate, and the solvent was removed by evaporation. Excess aldehyde was removed by distillation at an oil bath temperature of 220° and a pressure of 0.5 mm. The residue was dissolved in benzene and some impurities were thrown out by addition of isopropyl ether. The solvent was removed by distillation and the canary yellow product was crystallized four times from ethyl acetate; yield 3.0 g., 10%, m.p. 118°.[10]

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61. Found: C, 83.06, 82.95; H, 6.60, 6.77.[11]

1-(p-Diethylaminostyryl)isoquinoline (IIe). A mixture containing 10 g. (0.07 mole) of 1-methylisoquinoline, 23 g. (0.13 mole) of *p*-diethylaminobenzaldehyde, and 9.5 g. (0.07 mole) of anhydrous zinc chloride was heated 24 hr. at 115–120°. The mixture was extracted with chloroform. The chloroform solution was washed with 8*N* sodium hydroxide, then with water, and dried over sodium sulfate. Solvent and unreacted benzaldehyde were removed by vacuum distillation and the residue was dissolved in absolute ethanol. Addition of water and chilling several days produced yellow crystals which, after repeated recrystallization from ethanol and from isohexane, melted at 93°; yield 5 g., 24%.

Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33. Found: C, 83.39, 83.25; H, 7.11, 7.31.

1-(p-N-Morpholinostyryl)isoquinoline (IIf). A mixture of 1-methylisoquinoline 18.69 g. (0.131 mole) and 25 g. (0.131 mole) *p*-*N*-morpholinobenzaldehyde[12] was heated 2.5 hours at 270–275°, permitting water vapor to escape.[13] Repeated recrystallizations from ethyl acetate, from isopropyl ether, from isohexane, and from methanol yielded 5.86 g., 14%, 1-(*p*-*N*-morpholinostyryl)isoquinoline, dark yellow crystals, m.p. 149°.

Anal. Calcd. for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37. Found: C, 79.78, 79.52; H, 6.35, 6.43.

4-(p-Dimethylaminostyryl)quinoline (III). A mixture of 4.3 g. (0.030 mole) of 4-methylquinazoline,[14] 8.6 g. (0.058 mole) of *p*-dimethylaminobenzaldehyde and 2.2 g. (0.016 mole) of zinc chloride was heated 24 hr. at 120° in a glass stoppered bottle. Unreacted aldehyde was removed by extraction with boiling chloroform and the residue was treated with excess concentrated ammonium hydroxide to liberate the free base and dissolve zinc salts. The tarry material and ammonium hydroxide were kept in contact, with occasional stirring, over a period of four days. The residue was washed with water, allowed to dry at room temperature, then ground. The product was extracted with boiling methylpentanes in a Soxhlet extractor and recrystallized twice from methanol to give bright red crystals, m.p. 138°. Yield 12%.

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22. Found: C, 78.35, 78.58; H, 6.32, 6.20.

Department of Chemistry
Carson-Newman College
Jefferson City, Tenn.

(9) H. Erlenmeyer, H. Baumann, and E. Sorkin, *Helv. Chim. Acta*, **31**, 1978 (1948).

(10) All temperatures recorded are corrected.

(11) Analyses were carried out by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(12) E. I. du Pont de Nemours & Company, British Patent 607,920, Sept. 7, 1948.

(13) R. S. Tipson, *J. Am. Chem. Soc.*, **67**, 507 (1945).

(14) M. T. Bogert and F. P. Nabenhauer, *J. Am. Chem. Soc.*, **46**, 1932 (1924).

Some Tetrasubstituted Silanes Prepared by Free Radical Addition to Alkenes

R. H. Meen and Henry Gilman

Received October 18, 1956

A recent communication from this laboratory[1] has described the benzoyl peroxide-catalyzed addition of triphenylsilane to long-chain terminal-unsaturated alkenes. We have extended this synthesis to the addition of triphenylsilane to the ethylenic linkages of allyltriphenylsilane and diallyldiphenylsilane. In both cases low yields of completely saturated crystalline compounds were isolated. Unsaturation tests with bromine and with aqueous

(1) H. Merten and H. Gilman, *J. Am. Chem. Soc.*, **76**, 5798 (1954). This paper gives references to related free radical additions.

permanganate were negative. Although the structures of these products have not been proven we suggest structures based on addition of the triphenylsilyl radical to the terminal carbon atoms.

$$(C_6H_5)_3SiCH_2CH{=}CH_2 + (C_6H_5)_3SiH \xrightarrow{\text{peroxide}} (C_6H_5)_3SiCH_2CH_2Si(C_6H_5)_3$$

This reaction was attempted with triallylphenylsilane and with tetraallylsilane but as yet crystalline products have not been isolated.

It is noteworthy that a much cleaner reaction was obtained with triphenylgermane which added to allyltriphenylsilane in 76% yield.[2]

The compounds diallyldiphenylsilane and triallylphenylsilane were prepared by treatment of the appropriate chlorosilane with allylmagnesium bromide.[3] These reactions proceeded rapidly in refluxing ether solution which is in marked contrast to the sluggish reactions exhibited by most Grignard reagents in comparable reactions.[4]

EXPERIMENTAL[5]

Diallyldiphenylsilane. A solution of 0.448 mole of allylmagnesium bromide[6] in 350 ml. of ethyl ether was added to a solution of 47.2 g. (0.186 mole) of diphenyldichlorosilane in ethyl ether at such a rate that gentle refluxing occurred. A heavy precipitate formed during the addition. When 1.72 equivalents of the Grignard reagent had been added Color Test I[7] was negative, indicating a rapid reaction. The mixture was stirred under reflux for 12 hr. and then hydrolyzed with cold dilute hydrochloric acid. The ether layer was washed with water, dried over sodium sulfate and distilled, finally, at 1.2 mm., giving a main fraction of 25.1 g. (51%), b.p. 128–130°, n_D^{25} 1.5753, d_4^{25} 0.995.

Anal.[8,9] Calcd. for $C_{26}H_{20}Si$: Si, 10.6; M_D, 87.6. Found: Si, 10.8, 10.8; M_D 87.9.

Triallylphenylsilane. The preceding procedure was used with 0.696 mole of allylmagnesium bromide and 40.9 g. (0.194 mole) of phenyltrichlorosilane giving a main fraction of 33.6 g. (76%), b.p. 90–92° (0.8 mm.) n_D^{20}, 1.5339, d_4^{20} 0.924.

Anal. Calcd. for $C_{15}H_{10}Si$: Si, 12.3; M_D 76.6. Found: Si, 12.4, 12.4; M_D, 76.9.

1,3-bis(Triphenylsilyl)propane. A mixture of 4.81 g. (0.016 mole) of allyltriphenylsilane,[10] 26.0 g. (0.10 mole) of triphenylsilane, 0.32 g. (0.0013 mole) of benzoyl peroxide, and 25 ml. of hexane was stirred in a 75° bath for 24 hr. Distillation gave a volatile fraction b.p. 110–135° (0.05 mm.) consisting of unchanged triphenylsilane and 0.50 g. (10%) of unchanged allyltriphenylsilane. The residue from the distillation was a viscous liquid. Dilution with a few milliliters of benzene and 50 ml. of absolute ethanol gave 1.1 g. of a solid melting at 123–132°, after several days at 0°. Repeated recrystallizations from benzene–absolute ethanol, *n*-propyl alcohol, and acetone gave 0.09 g. (1%) of crystals melting at 150–152°.

Anal.[11] Calcd. for $C_{39}H_{36}Si_2$: Si, 10.0. Found: Si, 10.2, 10.3.

When this procedure was repeated in a quartz flask at 45° with ultraviolet irradiation in place of the peroxide none of the product could be isolated.

Diphenyl-bis(3-triphenylsilylpropyl)silane. When 2.20 g. (0.0083 mole) of diallyldiphenylsilane was treated with 26.0 g. of triphenylsilane using peroxide catalyst as in the preceding experiment, there was obtained 0.61 g. (9%) of a solid melting at 108–111° after crystallization from *n*-propyl alcohol. Recrystallization from petroleum ether (b.p. 100–120°) gave 0.30 g. (5%) of crystals m.p. 115–117°.

Anal. Calcd. for $C_{54}H_{52}Si_3$: Si, 10.7. Found: Si, 10.7, 10.7.

1-Triphenylsilyl-3-triphenylgermanylpropane. A mixture of 2.40 g. (0.008 mole) of allyltriphenylsilane, 15.3 g. (0.05 mole) of triphenylgermane, 0.16 g. (0.00066 mole) of benzoyl peroxide, and 25 ml. of hexane was stirred at 75° for 24 hr. After distillation of unchanged triphenylgermane at 125–135° (0.05 mm.) there was obtained 5.3 g. of a viscous residue. Dilution with 12 ml. of petroleum ether (b.p. 60–70°) gave 4.52 g. (93%) of crystals that melted at 128–131°. Three recrystallizations from absolute ethanol–benzene gave 3.66 g. (76%) of crystals, m.p. 134–135°.

Anal. Calcd. for $C_{39}H_{36}GeSi$: $GeO_2 + SiO_2$, 27.2. Found: $GeO_2 + SiO_2$, 27.4, 27.4.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

(2) Dr. R. Fuchs has already demonstrated in this laboratory that triphenylgermane adds to octene-1 to give triphenyl-*n*-octylgermane.

(3) A. D. Petrov and V. F. Mironov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 635 (1952) [*Chem. Abstr.*, **47**, 10471 (1953)] have described the preparation of triallylphenylsilane by the simultaneous addition of phenyltrichlorosilane and allyl bromide to magnesium.

(4) See H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.*, **79**, 1245 (1957) for the high reactivity of allylmagnesium types to the azomethine linkage.

(5) All melting and boiling points are uncorrected. All reactions were carried out in an atmosphere of dry, oxygen-free nitrogen.

(6) H. Gilman and J. H. McGlumphy, *Bull. soc. chim. France* [4], **43**, 1322 (1928).

(7) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(8) Molar refractions were calculated from the values of A. D. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, **58**, 174 (1954).

(9) Silicon analyses were performed by the procedure of H. Gilman, B. Hofferth, H. W. Melvin, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5767 (1950).

(10) Prepared from triphenylchlorosilane and allylmagnesium bromide in accordance with directions provided by L. F. Cason and H. G. Brooks, in unpublished studies.

(11) Microdetermination of silicon, H. Gilman and L. S. Miller, *J. Am. Chem. Soc.*, **73**, 968 (1951).

Preparation of Alkylnaphthalenes

HENRY GILMAN, CECIL G. BRANNEN,[1] AND ROBERT K. INGHAM[2]

Received November 26, 1956

Incidental to the preparation of some organosilicon compounds, 1-*n*-butylnaphthalene was isolated in 40 to 60% yields when 1-naphthyllithium was prepared by halogen-metal interconversion between 1-bromonaphthalene and *n*-butyllithium. This result was not surprising since this type of coupling reaction has been observed frequently.

(1) Present address: Research Laboratories, Standard Oil Co. of Indiana, Whiting, Indiana.

(2) Present address: Department of Chemistry, Ohio University, Athens, Ohio.

A survey of the literature revealed considerable discrepancy in regard to the physical constants of the *n*-butylnaphthalenes.[3] Also, a search of the literature disclosed that there are very few synthetic methods for obtaining alkylnaphthalenes and related hydrocarbons in good yield. Some of the methods, particularly the Friedel-Crafts synthesis, leave much to be desired concerning the structure of the isolated product. The Wurtz-Fittig reaction apparently leaves the alkyl residue intact during the reaction but the yields are low.[3]

Methyl iodide is reported to react immediately with 1-naphthyllithium to give an 80% yield of 1-methylnaphthalene.[4] Experiments indicated the reaction of alkyllithium compounds with naphthyl halides to be a method of choice for the synthesis of authentic specimens of hydrocarbons. 1-*n*-Butylnaphthalene and 1-*n*-hexylnaphthalene were prepared in good yields by this procedure.

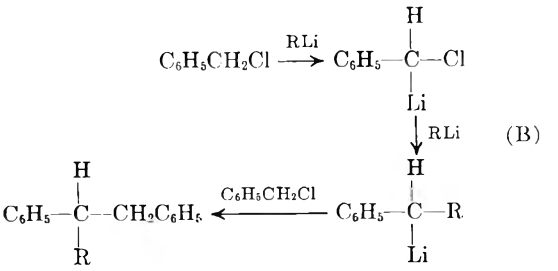
The following two facts leave little doubt that the formation of these alkylnaphthalenes proceeds as indicated in reaction sequence A. 1-Naphthoic acid is obtained in 90% yield by carbonating a mixture of 1-bromonaphthalene and *n*-butyllithium after the reagents have been stirred for 20 min.[5] Color Test II[6] becomes negative after the reaction mixture is stirred for 2 hr., while Color Test I[7] remains positive for 36 hr.

$$1\text{-}C_{10}H_7Br + RLi \longrightarrow 1\text{-}C_{10}H_7Li + RBr \longrightarrow 1\text{-}C_{10}H_7R + LiBr \quad (A)$$

R = *n*-alkyl

The reaction of benzyl chloride with 1-naphthyllithium failed to yield the expected 1-benzylnaphthalene. A colorless product, melting at 82–83°, was isolated; 1-benzylnaphthalene has a melting point of 58°.[8] The ultraviolet spectral curve of this compound showed four maxima, all of which are within 1 mμ of the maxima shown by 1-benzylnaphthalene. This evidence strongly suggests that the product is of the benzylnaphthalene type and not a phenylnaphthalene derivative. The latter type of compound shows a definite bathochromic shift due to the interaction of the two aromatic nuclei.

The reaction between phenyllithium and benzyl chloride is reported[9] to yield 1,1,2-triphenylethane and the proposed mechanism is summarized in reaction sequence B:



Wittig and Witt considered it more likely that diphenylmethane was formed as an intermediate but found that diphenylmethane was not metalated to any appreciable extent by phenyllithium. Assuming that a similar reaction occurred between 1-naphthyllithium and benzyl chloride, the end product, where R = 1-naphthyl, would be 1-naphthylphenylbenzylmethane.

Efforts to prepare 1-naphthylphenylbenzylmethane by other methods were unsuccessful. 2,3-Diphenylheptanoic acid is obtained by carbonating the mixture resulting from the addition of *n*-butyllithium to stilbene;[10] an attempt to prepare 2,3-diphenyl-3-(1-naphthyl)propionic acid, which could be decarboxylated to yield the desired compound, was not successful. Attempts were made to dehydrate 1-naphthylphenylbenzylcarbinol; the resulting ethylenic compound could then have been subjected to catalytic hydrogenation. Dehydration experiments with sulfuric acid and by Chugaev's method were futile. An attempt to prepare 1-naphthylphenylbenzylmethyl chloride, which subsequently could be reduced with lithium aluminum hydride, failed to yield the desired product.

EXPERIMENTAL[11]

1-n-Butylnaphthalene. To 101.5 g. (0.49 mole) of 1-bromonaphthalene was added an ethereal solution of 0.49 mole of *n*-butyllithium;[12] this mixture was allowed to reflux gently. After the exothermic reaction had subsided, the solution was heated to maintain reflux conditions until Color Test I[7] became negative (36 hr.). The mixture was hydrolyzed with water and the ether layer was washed with dilute hydrochloric acid. The solvent was removed from the dried organic layer and the residual oil was vacuum distilled; the main fraction (78.0 g., n_D^{20} 1.5805) boiled at 136–143° (3.5 mm.). Careful fractionation of this material through a column of 11 theoretical plates gave 71.0 g. (79%) of a colorless oil, b.p. 287–288° (745 mm.), n_D^{20} 1.5812, d_{20}^{20} 0.978. These physical constants are in good agreement with the published values.[3]

The *sym*-trinitrobenzene complex was prepared[3] by mixing and fusing equivalent quantities of the two reactants to obtain a yellow solid melting at 72–74°. A mixture melting point with the corresponding complex of 2-*n*-butylnaphthalene[13] (m.p. 75°) showed a large depression.

(3) The literature is reviewed by A. S. Bailey, G. B. Pickering, and H. C. Smith, *J. Inst. Petroleum*, **35**, 103 (1949).

(4) H. Gilman and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 1843 (1940).

(5) H. Gilman and C. G. Brannen, *J. Am. Chem. Soc.*, **73**, 4640 (1951).

(6) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940).

(7) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(8) G. Egloff, *Physical Constants of Hydrocarbons*, Reinhold Publishing Corp., New York, N. Y., 1947, Vol. IV, p. 227.

(9) G. Wittig and H. Witt, *Ber.*, **74**, 1474 (1941).

(10) K. Ziegler, F. Crössman, H. Kleiner, and O. Schäfer, *Ann.*, **473**, 1 (1929).

(11) All melting points and boiling points are uncorrected.

(12) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(13) Kindly supplied by A. S. Bailey, The Dyson Perrins Laboratory, Oxford University, England.

This experiment was repeated in essentially the same manner except that a 20% excess of *n*-butyl bromide was added to the refluxing solution immediately after the *n*-butyllithium and 1-bromonaphthalene were mixed. It was necessary to reflux the reaction for only 24 hr. before Color Test I was negative. The product was worked up and purified as before to obtain an 87% yield of the pure 1-*n*-butylnaphthalene.

In another run, the ether was replaced by benzene immediately after the *n*-butyllithium had been added. Color Test I was negative after refluxing the mixture for 15 hr., but the yield of pure product was only 38%.

1-n-Hexylnaphthalene. An ethereal solution of 0.41 mole of *n*-hexyllithium was prepared by the usual method[12] in 70% yield and was added to 85.0 (0.41 mole) of 1-bromonaphthalene. A 20% excess of 1-bromohexane was then added; even after refluxing the mixture for 5 days, Color Test I remained positive. The mixture was poured onto a dry ice–ether slurry and the acid was isolated in the customary manner by basic extraction. A 4.2% yield of 1-naphthoic acid (mixture melting point) melting at 155–156° was obtained. The neutral ether solution was worked up by fractional distillation in essentially the same manner as that described above for 1-*n*-butylnaphthalene to obtain a 61% yield of 1-*n*-hexylnaphthalene, n_D^{25} 1.5652, d_{20}^{20} 0.957. These physical constants are in good agreement with the reported values:[3] n_D^{20} 1.5652, d_4^{20} 0.958.

Reaction of 1-naphthyllithium with benzyl chloride. To 207.1 g. (1.0 mole) of 1-bromonaphthalene was added, at −5°, an ethereal solution containing 1.0 mole of *n*-butyllithium; the mixture was stirred for 30 min. and then 190 g. (1.5 moles) of freshly distilled benzyl chloride was slowly added. Color Test I was negative immediately after all of the benzyl chloride had been added. After pouring into water and separating the layers, the organic material was distilled at reduced pressure. The fraction boiling from 250–270° (3.5 mm.) was digested with petroleum ether (b.p. 30–60°) and the solution was allowed to crystallize undisturbed. After 2 days, 33 g. of white solid melting at 81–83° was removed. Recrystallization from ethanol raised the melting point to 82–83°.

The expected product, 1-benzylnaphthalene, melts at 58°.[8] A sodium fusion test showed halogen to be absent. The compound was insoluble in concentrated sulfuric acid, and a picrate could not be made. The ultraviolet absorption spectrum of the compound showed maxima at 273, 283.5, 292.5 and 276 mμ. On the basis of these data and the report by other investigators of a similar reaction,[9] the compound is believed to be 1-naphthylphenylbenzylmethane.

Anal. Calcd. for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.86, 93.96; H, 5.99, 6.21.

Attempted addition of 1-naphthyllithium to stilbene. An ethereal solution of 5.0 g. (0.028 mole) of stilbene and 0.056 mole of 1-naphthyllithium (prepared in 86% yield) was refluxed for 16 hr. Following hydrolysis and separation of the layers, the organic material was distilled at 3.0 mm. The fraction boiling from 240–305°, a red oil, was digested with 4 ml. of petroleum ether (b.p. 30–60°) and cooled to give 2.3 g. of stilbene (mixture melting point) melting at 118–120°. The remaining oil was dissolved in petroleum ether (b.p. 30–60°) and the petroleum ether solutions were combined and chromatographed on alumina. Six distinct bands developed on the column. After extruding and separating the 6 bands, the organic material was eluted with methanol. Evaporation of all fractions gave only colored oils which could not be crystallized.

1,2-Diphenyl-1-(1-naphthyl)ethylene (attempted). A number of substituted stilbenes have been prepared by distilling the corresponding carbinol at reduced pressure in the presence of a trace of sulfuric acid.[14] 1-Naphthylphenylbenzylcarbinol, m.p. 148–149°, was prepared by the method of Bauer.[15] Seven grams (0.021 mole) of 1-naphthylphenylbenzylcarbinol was distilled at 0.1 mm., after adding 3 drops of 50% sulfuric acid to the dry solid. The fraction boiling at 215–220°, 6 g. of a yellow viscous oil, was collected and dissolved in petroleum ether (b.p. 60–80°). Only oils were obtained from methanol, ethanol, petroleum ether, and various combinations of these solvents.

Attempted dehydration of 1-naphthylphenylbenzylcarbinol by Chugaev's method. Although this reaction was carried out in essential accordance with the procedure of Alexander and Mudrak[16] for use with a similar carbinol, a 92% recovery of starting alcohol was obtained. Since it was believed that the sodium salt of the carbinol was not formed initially in the 3-step reaction, the lithium salt was made by adding an equivalent amount of *n*-butyllithium to the alcohol. The above procedure was then followed but an 84% recovery of the carbinol was obtained.

1-Naphthylphenylbenzylmethyl chloride (attempted). A mixture of 2.0 g. (0.006 mole) of 1-naphthylphenylbenzylcarbinol and thionyl chloride (freshly distilled from quinoline) in benzene was refluxed for 2 hr. The solvent and excess thionyl chloride were removed by distillation at reduced pressure to give a yellow oil. This material could not be crystallized from petroleum ether (b.p. 60–80°), ethanol, or benzene.

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(14) W. Tadros, K. Farahat, and J. M. Robson, *J. Chem. Soc.*, 439 (1949).

(15) H. Bauer, *Ber.*, **42**, 2588 (1909).

(16) E. R. Alexander and A. Mudrak, *J. Am. Chem. Soc.*, **72**, 1810 (1950).

An Improved Metalation Procedure for Dibenzofuran

HENRY GILMAN AND RICHARD D. GORSICH

Received December 14, 1956

Dibenzofuran has been metalated successfully in the past with various organolithium compounds.[1] A comparative metalation study of dibenzofuran with *n*-butyllithium has been carried out in diethyl ether, di-*n*-butyl ether and petroleum ether (b.p. 28–38°) to give yields of 56%, 76%, and 1%, respectively, of 4-dibenzofurancarboxylic acid after carbonation of the metalated product. In all of these cases the reaction mixtures were refluxed for 4–24 hr. with the yields of 4-dibenzofuryllithium increasing slightly with increased refluxing periods.[2] The use of organolithium compounds other than *n*-butyllithium generally results in smaller yields of 4-dibenzofuryllithium.[2,3] It might be mentioned that 4-dibenzofuryllithium has been derived in rather good yields with *O*-methylhydroxylamine and with oxygen to give the amine and hy-

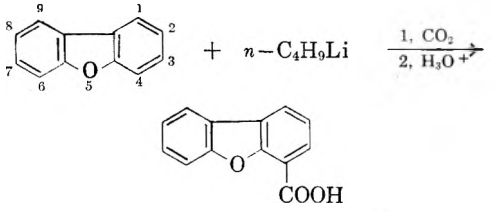
(1) For a general discussion of metalation reactions see H. Gilman and J. W. Morton, Jr., *Org. Reactions*, VIII, Chap. 6 (1954).

(2) H. Gilman, F. W. Moore, and O. Baine, *J. Am. Chem. Soc.*, **63**, 2479 (1941).

(3) H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **67**, 877 (1945).

droxy compound, respectively.[4] Although the yields of the latter two compounds were higher than that of the corresponding carboxylic acid, the conditions for preparing the 4-dibenzofuryllithium were quite similar.

We have metalated dibenzofuran with *n*-butyllithium in yields (83–86%) higher and under conditions much milder than ever described previously. The *n*-butyllithium, prepared in diethyl ether, was



added to a tetrahydrofuran solution of dibenzofuran at −60° and then the reaction mixture was stirred between 0–5° for 1 hr. before carbonating. For our present investigations we have purposely selected tetrahydrofuran because it is a more basic solvent than any utilized in previous studies.[5]

In order to examine further the pronounced effect of tetrahydrofuran on the metalation of dibenzofuran, a run was made at −50°. A significant 11% yield of acid was obtained after stirring at −50° for 1 hr. followed by carbonation. In contrast, a diethyl ether solution of dibenzofuran and butyllithium stirred at 0° for 1 hr. afforded only a 5% yield of acid.

It was hoped that the exclusion of diethyl ether from the reaction might result in the metalation occurring under even milder conditions than already mentioned. For this purpose the *n*-butyllithium was prepared *in situ* at −25° from butyl chloride.[6,7] The highest yield of acid obtained with this method was 30%. The use of butyl bromide instead of butyl chloride did not result in any better yields. The studies are being extended to other systems.

EXPERIMENTAL[8]

Metalation of dibenzofuran in tetrahydrofuran with preformed n-butyllithium (A) at 0°. To a stirred solution of 4.2 g. (0.025 mole) of dibenzofuran in 35 ml. of tetrahydrofuran[9] was added, during 10 min., 22 ml. of a diethyl ether solution containing 0.03 mole of *n*-butyllithium.[10] The temperature of the reaction mixture was maintained between −55 and −60° during the addition. On completion of the addition, the mixture was stirred between −45 and −50° for 5 min. before being allowed to warm to 0° during 15 min. The brown solution was stirred in an ice bath for 1 hr., cooled to −50° and carbonated by pouring the solution jetwise into a slurry of Dry-Ice and ether. Prior to separation of the two layers, 50 ml. of diethyl ether was added to the mixture to reduce the solubility of water in the organic layer. The aqueous layer was boiled until most of the tetrahydrofuran had been expelled and then was acidified with concentrated hydrochloric acid. The organic layer was extracted with two 30-ml. portions of 5% sodium hydroxide. The combined extracts were boiled and acidified. The combined crude acid was dried and then crystallized from a mixture of ethanol and water to give 4.56 g. (86%) of 4-dibenzofurancarboxylic acid, m.p. 213–214°. A mixed melting point with an authentic sample showed no depression. After drying the organic layer over anhydrous sodium sulfate and distilling the solvents, no unchanged dibenzofuran was recovered.

In another run the reaction mixture was stirred at 0° for 2.5 hr. After working up the mixture as described above there was obtained an 83% yield of the acid.

At −50°. In another experiment the temperature was kept between −55 and −60° during the addition. After completing the addition, the mixture was stirred at the minimum temperature afforded by dry ice-acetone for 15 min., and then between −50 and −55° for 70 min. The mixture was cooled to −70° and carbonated in the manner described in the preceding experiment. Work-up of the reaction mixture as described in the last run yielded 0.65 g. of crude acid melting over the range 208–212°. Crystallization from ethanol-water gave 0.58 g. (11%) of 4-dibenzofurancarboxylic acid, m.p. 212–214°. The yield of unchanged dibenzofuran was 3.41 g. (81%).

In a similar run employing the same quantities of reactants, the reaction mixture was stirred between −35 and −40° for 15 min. after adding the butyllithium during 9 min. at the same temperature. From the aqueous layer and basic extracts there was finally obtained 0.42 g. (7.9%) of acid, m.p. 212.5–214°. Distillation of the solvents from the organic layer left 3.80 g. (90%) of unchanged dibenzofuran.

Metalation of dibenzofuran with n-butyllithium prepared in situ. To a mixture of 0.60 g. (0.086 g. atom) of lithium wire cut into small pieces, 4.2 g. (0.025 mole) of dibenzofuran, and 40 ml. of tetrahydrofuran was added, during 18 min., a solution of 2.60 g. (0.028 mole) of *n*-butyl chloride in 5 ml. of tetrahydrofuran. The addition was carried out between −25 and −30°. The mixture became bright orange after adding a few drops of butyl chloride. Subsequent to stirring between −25 and −30° for 13 min., 20 ml. of diethyl ether was added; the mixture was cooled to about −60° and carbonated as described previously. Work-up of the reaction mixture in the usual manner gave 1.64 g. of crude acid which was recrystallized to give 1.60 g. (30%) of 4-dibenzofurancarboxylic acid, m.p. 210–212°.

There was obtained from the neutral organic layer 1.62 g. (39%) of starting material.

In a similar run *n*-butyl bromide was used in place of *n*-butyl chloride and the reaction mixture was stirred be-

(4) H. Gilman and R. K. Ingham, **75**, 4843 (1953); H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **57**, 1121 (1935).

(5) The base strength of tetrahydrofuran toward boron trifluoride is greater than that of diethyl ether; H. C. Brown and R. M. Adams, *J. Am. Chem. Soc.*, **64**, 2557 (1942).

(6) The butyllithium was prepared in this manner to avoid loss of the RLi compound. It has been observed that the yield of butyllithium decreases more rapidly in tetrahydrofuran than in diethyl ether; B. Gaj, unpublished studies.

(7) The mixture was not warmed to 0° since it is possible to cleave dibenzofuran with lithium in tetrahydrofuran at warmer temperatures; H. Gilman and J. J. Dietrich, *J. Org. Chem.*, in press.

(8) All reactions were carried out in an atmosphere of dry, oxygen-free nitrogen and all melting points are uncorrected.

(9) The tetrahydrofuran was dried and purified by shaking with sodium hydroxide pellets, refluxing over sodium metal for several hours and finally distilling, immediately before use, from lithium aluminum hydride.

(10) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949). The yield was determined according to a procedure described by H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

tween −30 and −35° for 35 min. rather than between −25 and −30°. In this run the yield of 4-dibenzofurancarboxylic acid was 1.32 g. (25%).[11]

From the neutral organic layer there was isolated 2.51 g. (60%) of starting dibenzofuran.

Metalation of dibenzofuran in diethyl ether at 0°. Twenty milliliters of a diethyl ether solution containing 0.028 mole of butyllithium was added rapidly to a stirred solution of 4.2 g. (0.025 mole) of dibenzofuran in 35 ml. of dry diethyl ether cooled to *ca.* −10°. The reaction mixture was stirred in an ice bath for 1 hr., cooled to −20° and carbonated. Work-up in the usual manner afforded 0.26 g. (4.9%) of 4-dibenzofurancarboxylic acid, m.p. 210–212°.

The organic layer, after drying and distilling the ether, gave 3.32 g. (79%) of starting dibenzofuran.

Acknowledgment. The authors wish to express their appreciation to the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, for financial assistance.

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(11) The low yield of acid obtained when using butyl bromide may be due in part to the tendency of butyl bromide to couple in tetrahydrofuran. Butyllithium can be prepared only in very small yields from butyl bromide and lithium in tetrahydrofuran; B. Gaj, unpublished studies.

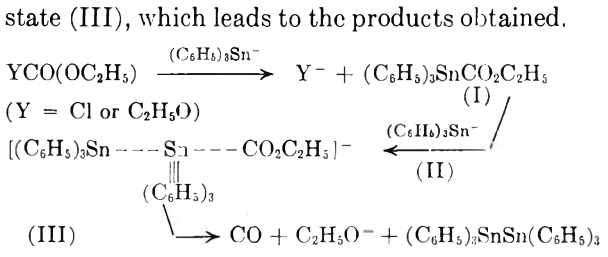
Reaction of Triphenyltin-Lithium with Some Esters

HENRY GILMAN AND LEWIS A. GIST, JR.[1]

Received January 23, 1957

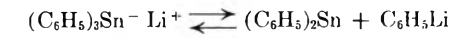
In the course of investigations in this laboratory, the reactions of triphenyltin-lithium with diethyl carbonate and with ethyl chloroformate have been explored as a possible route for preparing ethyl triphenylstannylcarboxylate and bistriphenyltin ketone. The products obtained, however, were not the desired ester and ketone. Instead, carbon monoxide was vigorously evolved, and hexaphenylditin was obtained as the principle product along with a lesser amount (*ca.* 20%) of tetraphenyltin.

The mechanism of this reaction was not determined. It is believed, however, that ethyl triphenylstannylcarboxylate was first formed, then decarbonylated in a manner similar to that proposed earlier for esters of triphenylsilanecarboxylic acid,[2] and for methyl triphenylgermanecarboxylate.[3] The proposed mechanism would involve the attack of the triphenyltin anion (II) on the tin atom of the intermediate ethyl triphenylstannylcarboxylate (I) with the formation of a transition state (III), which leads to the products obtained.



It is reasonable to expect the intermediate ethyl triphenylstannylcarboxylate to be rather unstable in the presence of a base. The electropositive triphenyltin radical attached directly to a pseudo-positive carbon atom should be highly susceptible to an anionic attack of this type. Furthermore, the large atomic radius of the tin atom coupled with its low electron density renders it vulnerable to nucleophilic attack. It is also possible that a radical mechanism might be proposed for this reaction.

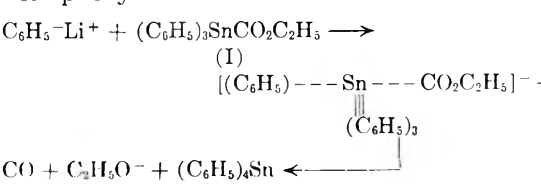
After carbonation of the product obtained from the reaction of triphenyltin-lithium with fluorene, d'Ans and co-workers[4] obtained approximately a 20% yield of 9-fluorenecarboxylic acid. These investigators[4] concluded, therefore, that triphenyltin-lithium was approximately 20% dissociated according to the equation:



Conversely, the reactions of triphenyltin-lithium with gaseous carbon dioxide, Dry Ice, benzophenone, and benzalacetophenone were investigated in this laboratory earlier,[5,6] and no evidence of such an equilibrium could be found.

The reaction of triphenyltin-lithium with diethyl carbonate and with ethyl chloroformate offered an opportunity to investigate again the possibility of this equilibrium. None of the compounds which might be expected from the reaction of phenyllithium with diethyl carbonate or with ethyl chloroformate could be found among the products of the reaction.

The presence of tetraphenyltin in these reaction mixtures could conceivably have resulted from the reaction of ethyl triphenylstannylcarboxylate (I) with phenyllithium as follows:



However, tetraphenyltin is believed to have resulted as a by-product in the preparation of triphenyltin-lithium, and not from a reaction of the type proposed above, since it is invariably obtained

(1) General Education Board Fellow at Iowa State College, 1952–1954.

(2) A. G. Brook and H. Gilman, *J. Am. Chem. Soc.*, **77**, 2322 (1955).

(3) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, **77**, 4675 (1955).

(4) J. d'Ans, H. Zimmer, E. Endrulat, and K. Lübke, *Naturwissenschaften*, **39**, 450 (1952).

(5) H. Gilman and S. D. Rosenberg, *J. Org. Chem.*, **18**, 680 (1953).

(6) H. Gilman and S. D. Rosenberg, *J. Org. Chem.*, **18**, 1554 (1953).

in yield of 15–20% in the hydrolysis of triphenyltin-lithium.[6] Furthermore, the reaction of phenyllithium (as well as phenylmagnesium bromide) with methyl triphenylgermanecarboxylate has been investigated,[7] and the product obtained was triphenylgermyldiphenylcarbinol, rather than tetraphenylgermane.

It has been concluded, therefore, that the ability of triphenyltin-lithium to act as a metalating agent cannot be precluded in interpreting the results obtained by d'Ans and co-workers[4] since no evidence of an equilibrium has been obtained in any of the reactions of triphenyltin-lithium with carbonyl systems.

EXPERIMENTAL

All melting points reported here are uncorrected. For compounds melting below 250°, the determinations were made in a silicone-oil bath with a 250° thermometer. For high melting compounds a copper block equipped with a 520° thermometer was employed.

Triphenyltin-lithium. Triphenyltin-lithium was prepared through the reaction[8] of phenyllithium with anhydrous tin (II) chloride. A typical 0.045 mole preparation of triphenyltin-lithium was treated with a solution of 13.3 g. (0.045 mole) of triphenylchlorosilane in 100 ml. of ether according to the method previously described.[5,6] After hydrolysis, 19.6 g. (73%) of crude triphenylsilyltriphenyltin was obtained, melting over the range of 277–285°. This compound was recrystallized from benzene to produce 17.7 g. (65%) of pure triphenylsilyltriphenyltin, melting at 287–289°. A mixture melting point with an authentic specimen was not depressed. This experiment indicates the presence of triphenyltin-lithium in a minimum yield of 65%.

Triphenyltin-lithium with diethyl carbonate. Run I. A solution of 2.36 g. (0.02 mole) of diethyl carbonate in 10 ml. of ether was added rapidly to an ethereal suspension of 0.01 mole of triphenyltin-lithium at −10°. Immediately after this addition, a gas was evolved vigorously which blackened a piece of filter paper moistened with a dilute solution of palladium chloride,[9] thus indicating that the gas was carbon monoxide. The stirred reaction mixture was allowed to come to room temperature, and then stirred at room temperature for 1 hr. The mixture was then poured slowly into aqueous ammonium chloride, the insoluble product was removed by filtration, and the two layers were separated. The insoluble product removed after hydrolysis was recrystallized from benzene to obtain 0.55 g. (14%) of tetraphenyltin, melting at 224°. The ethereal layer was dried, then concentrated to obtain 2.01 g. of amorphous material melting over the range 194–207°. Fractional crystallization of this mixture from carbon disulfide, followed by recrystallization of the fractions from benzene gave 1.40 g. (40%) of hexaphenylditin, melting at 231–232°, and 0.32 g. (8%) of additional tetraphenyltin, melting at 222–223°. The total yield of tetraphenyltin was 22%. Mixture melting points with authentic specimens in each case were not depressed.

No evidence of ethyl benzoate, benzophenone or benzoic acid could be found.

Run II. This reaction did not differ essentially from the one described above except in the size of the run. From the reaction of 0.045 mole of triphenyltin-lithium with 10.6 g. (0.09 mole) of diethyl carbonate essentially the same results were obtained. Carbon monoxide was evolved vigorously (palladium chloride test). After hydrolysis and purification of the products, 7.8 g. (50%) of hexaphenylditin, melting at 230–231°, and 3.46 g. (19.5%) of tetraphenyltin, melting at 221–223° were obtained.

No evidence of ethyl benzoate, benzophenone, or benzoic acid could be found.

Triphenyltin-lithium with ethyl chloroformate. Run I. A solution of 9.7 g. (0.09 mole) of freshly distilled ethyl chloroformate in 25 ml. of ether was added all at once to an ethereal suspension containing 0.045 mole of triphenyltin-lithium at room temperature. Carbon monoxide was vigorously evolved (palladium chloride test). The reaction mixture was stirred at room temperature for a period of 2 hr., then hydrolyzed with water, and the products were isolated in the same manner as was described in the reaction of triphenyltin-lithium with diethyl carbonate. After first separating the products by fractional crystallization from carbon disulfide, they were recrystallized from benzene, to produce 1.3 g. (9.2%) of tetraphenyltin and 8.1 g. (51%) of hexaphenylditin. The products obtained melted at 220–222° and 226–227° respectively, and mixture melting points with authentic specimens were not depressed.

No other products were found in the reaction mixture.

Run II. This reaction was carried out under exactly the same conditions as the reaction described in *Run I*, with the single exception that the reversed order of addition was used; *i.e.*, the 0.045 mole of triphenyltin-lithium suspended in ether was added gradually to 9.7 g. (0.09 mole) of ethyl chloroformate in 25 ml. of ether. After hydrolysis, fractional crystallization, and recrystallization as described above, 1.6 g. (11%) of tetraphenyltin and 8.6 g. (54%) of hexaphenylditin were obtained. These products melted at 220–222° and 228–230° respectively.

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(7) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, **77**, 5740 (1955).

(8) H. Gilman and S. D. Rosenberg, *J. Am. Chem. Soc.*, **74**, 531 (1952).

(9) R. Nowicki, *Chem. Ztg.*, **35**, 1120 (1911).

Polynitrogen Systems from the Hydrazinocarbonic Acids. Part VIII.[1] The Synthesis and Estimation of Some Nitroguanylhydrazones

F. L. SCOTT,[2] W. N. MORRISH, AND J. REILLY

Received October 25, 1956

The use of nitroaminoguanidine as a reagent for the characterization of carbonyl compounds[3] has been extended in this present note. In addition an effort was made to utilize the Jamieson iodate technique[4] to estimate some nitroguanylhydrazones.

(1) Part VII, This Series, F. L. Scott, F. C. Britten and J. Reilly, *J. Org. Chem.*, **21**, 1191 (1956).

(2) To whom inquiries concerning reprints are to be sent. Present address, Department of Chemistry, University of California, Los Angeles 24, Calif.

(3) Compare (a) R. A. Henry and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 278 (1952); (b) W. F. Whitmore, A. J. Revukas, and G. B. L. Smith, *J. Am. Chem. Soc.*, **57**, 706 (1935); (c) G. B. L. Smith and E. P. Shoub, *J. Am. Chem. Soc.*, **59**, 2077 (1937); (d) W. D. Kumler and P. P. T. Sah, *J. Am. Pharm. Assoc.*, **41**, 375 (1952).

(4) (a) G. I. Keim, R. A. Henry, and G. B. L. Smith, *J. Am. Chem. Soc.*, **72**, 4944 (1950); (b) R. A. Henry, R. C Makosky, and G. B. L. Smith, *J. Am. Chem. Soc.*, **73**, 474 (1951).

The procedure employed involved hydrolysis by acid of the hydrazones followed by titrimetric determination of the liberated hydrazine function with standard iodate solution. With this technique we found it possible to titrate within ±1% both furfuraldehyde and 4-methoxybenzaldehyde nitroguanylhydrazones. Both of these hydrolyses began very rapidly then slowed and required approximately 9 days to reach an endpoint. Under this same analytical procedure neither the acetone, benzaldehyde, (4-methoxy-3-hydroxy)- or (2-hydroxy)benzaldehyde nitroguanylhydrazones afforded satisfactory titers.[5] Part of these latter anomalously low results may be caused by an internal oxidation-reduction reaction which dissipates the hydrazine function of nitroaminoguanidine. A trial run to confirm this possibility revealed that nitroaminoguanidine in strongly acidic aqueous solution at *ca.* 100° lost its hydrazine function at an approximate rate of 2×10^{-3} sec.$^{-1}$ Under the chosen hydrazone hydrolysis conditions this hydrazine dissipation rate is undoubtedly much slower (the rate being $< 1 \times 10^{-7}$ sec.$^{-1}$ at room temperature) but where the hydrazone hydrolysis rate is comparably slow then loss of hydrazine function becomes evident as a complicating factor in the iodate analyses.

EXPERIMENTAL[6]

Nitroguanylhydrazones. Nitroaminoguanidine was prepared by the method of Henry, Makosky, and Smith.[4b] The new hydrazones synthesized were prepared by the standard methods already described in the literature and are summarized in Table I.

Hydrolysis experiments. The following exemplifies the technique employed. To 0.1002 g. of furfuraldehyde nitroguanylhydrazone were added 20 ml. of water, 30 ml. of concentrated hydrochloric acid, and 10 ml. of chloroform.[7] A few ml. of 0.1*N* potassium iodate solution (standardized against reagent grade hydrazine sulfate), were run in, the mixture was vigorously shaken, and then more iodate was added, dropwise, until the purple color, which had developed in the chloroform layer, had disappeared. The mixture was maintained in a dark press, its temperature being maintained at 15 ± 1°C., and, periodically, further aliquots of standard iodate solution were added, the accepted endpoint each time being a colorless chloroform layer. During each addition, the mixture was well agitated. After nine days, a final titer of iodate equivalent to 0.0600 g. of nitroaminoguanidine was obtained. The calculated quantity of nitroaminoguanidine to be liberated was 0.0605 g. Several repeat experiments with this same hydrazone again afforded accuracy of assay to within ±1%. As already mentioned, the 4-methoxybenzylidene analogue (again with a nine-day period required for attainment of final endpoint), also had the experimental and calculated iodate titers within ±1%. The 2-hydroxybenzylidene nitroguanylhydrazone after 28 days had only liberated approximately half the calculated

TABLE I

SOME NITROGUANYL HYDRAZONES

Carbonyl Compound	Product Formula	Physical Appearance	M.p., °C.	Yield, %	Analyses					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Acraldehyde	$C_4H_7N_5O_2$	Cream-colored powder[a]	165	77	30.6	30.6	4.5	4.4	—	—
Alloxane	$C_6H_9N_7O_7$[b]	Salmon-colored powder[c]	198[d]	90	21.5	21.7	3.2	3.2	—	—
Alloxane	$C_5H_5N_7O_5$	Brick-red powder[e]	251	90	24.7	24.8	2.1	2.4	40.3	40.0
4-Aminoacetophenone	$C_9H_{12}N_6O_2$	Yellow microcrystals[f]	203	90	45.8	45.7	5.1	5.0	35.6	35.2
Benzylidene acetone	$C_{11}H_{12}N_6O_2$	Ivory platelets[g]	181	91	53.4	53.6	5.3	5.2	—	—
2,4-Dinitrobenzaldehyde	$C_8H_7N_7O_6$	Cream powder[f]	240	97	32.3	32.9	2.4	2.4	33.0	32.6
Methyl benzyl ketone	$C_{10}H_{13}N_5O_2$	Colorless plates[h]	174[i]	92	51.1	50.9	5.5	5.5	—	—
Methyl nonyl ketone	$C_{12}H_{25}N_5O_2$	White microcrystals[g]	114[j]	80	53.1	52.8	9.2	9.2	—	—
3,4-Dihydroxybenzaldehyde	$C_8H_9N_5O_4$	Yellow flakes[e,f,k]	232	97	40.2	40.1	3.8	3.9	29.3	28.7
Pyruvic aldehyde	$C_5H_{10}N_{10}O_4$[l]	Yellow powder[h]	344[m]	92	21.9	21.5	3.7	3.8	51.1	50.9
2-Thiophene aldehyde	$C_6H_7N_5SO_2$	Lemon, fibrous needles[g]	199	87	33.8	34.2	3.3	3.1	32.9	32.4[n]
Terephthaldehyde	$C_{16}H_{12}N_{10}O_4$[l]	Yellow powder[o]	254[d,p]	92	35.7	36.0	3.6	3.9	—	—

[a] From 50% aqueous ethanol. [b] Physical data recorded are for the dihydrate. [c] Directly as isolated, under the standard conditions, without further purification. [d] Melts with decomposition. [e] From boiling water. [f] From aqueous acetic acid. [g] From 75% ethanol. [h] From absolute ethanol. [i] Darkens prior to melting. [j] Softens at 110°. [k] Photosensitive and readily oxidized. [l] Physical data recorded are for the dihydrazone. [m] Melts with explosive decomposition. [n] Calcd.: S, 15.0. Found: S, 14.9, 15.1. [o] Very insoluble, hence merely washed repeatedly with boiling water and boiling ethanol. [p] M.p. varies markedly with rate of heating.

(5) Similar difficulties in the estimation of benzaldehydehyde nitroguanylhydrazone have been mentioned in the interesting paper of W. R. McBride, R. A. Henry, and S. Skolnik, *Anal. Chem.*, **25**, 1042 (1953).

(6) All melting points are uncorrected. All microanalyses are by Drs. Wieler and Strauss, Oxford, England.

(7) Purified as described in A. I. Vogel, *A Textbook of Practical Organic Chemistry*, 2nd ed., page 174, Longmans, Green and Co., London, 1951.

quantity of nitroaminoguanidine and its final titer was *ca.* 30% too low. The 3-hydroxy-4-methoxy analogue prove impossible to analyze as after an eight-day period, the chloroform layer acquired a permanent red color which completely obscured the visual endpoint sought. The titrimetric endpoints obtained with both the acetone and benzaldehyde nitroguanylhydrazones were also some 40 and 20% too low respectively.[5] These low values suggested that perhaps nitroaminoguanidine had lost some of its hydrazine function under the given analysis conditions. A trial confirmed that this was possible. Thus, when a number of *ca.* 0.1 g. samples of nitroaminoguanidine, dissolved in 20 ml. of water and 30 ml. of concentrated hydrochloric acid were heated on a steam bath for varying periods of time (5–30 minutes), and then, after quenching the reaction by immersion of the reaction solutions in ice, titrated with iodate as before, a loss of hydrazine function with a rate constant of roughly 2×10^{-3} sec.$^{-1}$ was observed. Under conditions more closely related, temperature-wise, to the hydrazone hydrolyses but involving much greater time intervals (20–90 days) than the previous blank trials, nitroaminoguanidine was again discovered to undergo partial loss of hydrazine function. While this hydrazine dissipation may not be the sole cause of the anomalous iodate values, in any event it can demonstrably be accepted as a factor therein particularly with those hydrazones which prove slowest to hydrolyze.

CHEMISTRY DEPARTMENT
UNIVERSITY COLLEGE
CORK, IRELAND

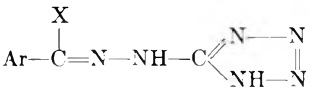
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
LOS ANGELES 24, CALIF.

Polynitrogen Systems from the Hydrazinocarbonic Acids. Part IX.[1] The Synthesis and Bromination of Some 5-Tetrazolyl- and Related -hydrazones

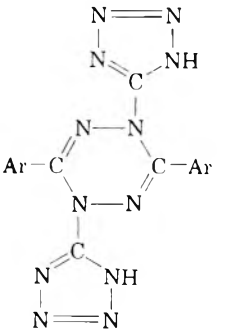
F. L. SCOTT,[2] W. N. MORRISH, AND J. REILLY

Received October 25, 1956

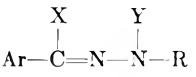
We have developed the utility of 5-hydrazinotetrazole as a means of characterizing carbonyl compounds somewhat more fully than the scattered literature data[3] thereon previously achieved. Some preliminary observations have also been made on the possibility of ω-bromination of the 5-tetrazolylhydrazones (I). The reactions encountered with the benzylidene derivative (IA) typify the complexities involved. When IA was brominated under the standard conditions utilized, namely, using equimolar quantities of bromine and hydrazone in glacial acetic acid solution (or suspension) at room temperature, it formed apparently the crude ω-bromo derivative (IB). This when crystallized from anhydrous chloroform was obtained pure. When it was boiled in glacial acetic acid, it dehalogenated and reverted to the parent hydrazone (IA). When refluxed in 50% aqueous ethanol for a few minutes IB was oxidized and the hydrogen-abstracted derivative so isolated may possibly be the tetrazine (IIA).[4] When IA was treated with an excess of bromine, again in glacial acetic acid medium, considerable hydrolysis of the hydrazone accompanied the ω-bromination effected. Finally, when IA was allowed to react in an excess of bromine without any additional solvent ring—as well as ω—bromination occurred, yielding most probably IC. The 3-nitrobenzylidene analogue of IA, *viz.*,



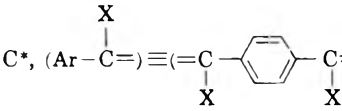
I, A, Ar = C_6H_5, X = H;
B, Ar = C_6H_5, X = Br;
C, Ar = 4(?)Br—C_6H_4, X = Br;
D, Ar = 3—NO_2—C_6H_4, X = H



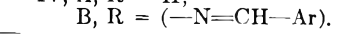
II, A, Ar = C_6H_5;
B, Ar = 3—NO_2—C_6H_4



III, A, X = Br, Y = H;
B*, R = C(=NH)—NH—NO_2;



D, X = H, Y = C(=O)—C_6H_5, R = C(=NH)—NH—C(=O)—C_6H_5;
E, X = NH_2, Y and R as in D;
For substances starred (*), X = Y = H



IV, A, R = H;
B, R = (—N=CH—Ar).

(1) Part VIII, F. L. Scott, W. N. Morrish, and J. Reilly, *J. Org. Chem.*, **22**, 690 (1957).

(2) To whom inquiries concerning reprints are to be sent. Present address, Department of Chemistry, University of California, Los Angeles 24, Calif.

(3) *Vide* (a) J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895); (b) J. Thiele and J. T. Marais, *Ann.*, **273**, 144 (1893); (c) J. Thiele, *Ann.*, **303**, 66 (1898); (d) K. A. Hofmann, H. Hock, and H. Kirmreuther, *Ann.*, **380**, 131 (1911); (e) F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Appl. Chem.*, **2**, 368 (1952).

(4) Compare: F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, **127**, 975, 1687 (1925); F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 157, 843 (1930); F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, 113 (1926); F. D. Chattaway, T. Deighton, and A. Adair, *J. Chem. Soc.*, 1925 (1931); F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 2787, 2792 (1931); F. D. Chattaway and H. Irving, *J. Chem. Soc.*, 90 (1935).

ID, also appeared to result in some of the appropriate tetrazine (IIB), under suitable reaction conditions. The complexities in the other tetrazolylhydrazone brominations have not been clarified as yet.

We have also examined as a cognate study the reactions of some representative acylhydrazones with bromine. These reactions which were again intended to provide access to the synthetically useful[4] ω-bromo derivatives (IIIA), were generally unsuccessful. Thus under the standard conditions described above the specific substituted aldehydic derivatives of diamonoguanidine (IVA),[5] triaminoguanidine (IVB), and nitroaminoguanidine (IIIB) employed were recovered unchanged. However, when one example of this last group, *viz.* IIIC, was allowed to react under forcing conditions some, though anomalous, reaction was detected. With an acylated guanylhydrazone, the dibenzoyl derivative (IIID), ω-bromination, detected *via* its aminolysis product the hydrazidine (IIIE), apparently did occur. However, with simpler monoaminoguanyl derivatives the bromination reactions involved were again complex. Finally when these hydrazone brominations were attempted at the reflux temperature of the (glacial acetic acid) solvent extensive decomposition of the hydrazone was observed.

EXPERIMENTAL[6]

5-Tetrazolylhydrazones. 5-Hydrazinotetrazole dihydrochloride was prepared by essentially the method of Thiele and Marais (*loc. cit.*). The following illustrates the general technique[*cf.* 3a] used in the preparation of its aldehydic derivatives. To 5.0 g. of 5-hydrazinotetrazole dihydrochloride, dissolved in 125 ml. of warm water containing 10 ml. of ethanol, was added 8.5 g. of sodium acetate trihydrate and, immediately following this, 2.9 ml. of cinnamaldehyde were run in, drop-wise, with constant agitation of the solution. An opalescent liquor resulted which on vigorous shaking deposited a thick mass of yellow-orange, colored material. The mixture was refluxed for a further 10 min. to ensure completion of reaction and then was allowed to cool. The yellow solid thus obtained weighed 4.84 g. (82% yield), m.p. 199–200°. The filtrate, on ether extraction, yielded a further quantity (0.08 g.) of the hydrazone. After 2 recrystallizations from 70% aqueous ethanol, and one from absolute ethanol, the cinnamaldehyde 5-tetrazolylhydrazone was obtained as golden yellow microcrystals, m.p. 207°.

Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.1; H, 4.7; N, 39.3. Found: C, 56.0; H, 4.5; N, 39.5.

The remaining derivatives prepared are summarized in Table I.

Hydrazone bromination attempts. The acylhydrazones whose reactions will be described first were themselves prepared by standard methods from the literature.

(*a*) *With aminoguanidine derivatives.* (1) A solution of 0.47 ml. of bromine in 28 ml. of glacial acetic acid was added, dropwise, to a well-stirred slurry of 2.0 g. of di-2-nitrobenzylidene diaminoguanidine in 100 ml. of the same solvent. On filtering, washing, drying, and recrystallizing the residual solid, it proved to be unchanged hydrazone (82% yield).

(5) The symbol subsequent to each hydrazide represents the substituted aldehydic hydrazone of the specific hydrazide.

(6) All melting points are uncorrected. All microanalyses are by Drs. Wieler and Strauss, Oxford, England.

TABLE I

NEW 5-TETRAZOLYLHYDRAZONES

Carbonyl Compound	Product Formula	Physical Appearance	M.p., °C.	Yield, %	Analyses					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found[e]
4-Chlorobenzaldehyde	$C_8H_7N_6Cl$	Short, colorless needles	233	98	43.1	43.1	3.1	3.4	37.8	37.8[a]
3,4-Dimethoxy benzaldehyde	$C_{10}H_{12}N_6O_2$	Fibrous needles	217	97	48.4	47.8	4.8	4.6	33.9	34.4[b]
2,3-Dimethoxy benzaldehyde	$C_{10}H_{12}N_6O_2$	Soft, amorphous powder	212	98	48.4	48.3	4.8	4.7	33.9	34.4[c]
4-Isopropyl benzaldehyde	$C_{11}H_{14}N_6$	White plates	227	92	57.4	57.6	6.1	6.3	36.5	36.2
2-Hydroxy benzaldehyde	$C_8H_{10}N_6O_2$[d]	Ivory granules	212	98	43.2	43.6	4.5	4.7	37.8	38.2
2-Nitro benzaldehyde	$C_8H_7N_7O_2$	Fine yellow granules	245[g]	96	41.2	41.1	3.0	2.6	42.1	42.0
3-Nitro benzaldehyde	$C_8H_7N_7O_2$	White microcrystals	250	99	41.2	41.5	3.0	3.3	42.1	42.3
3-Hydroxy-4-methoxy benzaldehyde	$C_9H_{12}N_6O_3$[d]	Yellow microcrystalline powder	212	100	42.9	42.4	4.8	4.8	33.3	33.7

[a] Calcd.: Cl, 16.0. Found: Cl, 15.7. [b] Calcd.: OCH_3, 25.0. Found: OCH_3, 25.1. [c] Calcd.: OCH_3, 25.0. Found: OCH_3, 24.8. [d] The physical data recorded are for the monohydrate. [e] Starts to decompose at 200°, darkens and begins to sublime at 225°. [f] Purified in the absence of light, this substance is white. It rapidly turns yellow with light exposure.

Evaporation of the acetic acid filtrate to dryness, *in vacuo*, at 30° afforded a further 15% yield of unchanged hydrazone. Two other analogous substances, dibenzylidene and di-3-nitrobenzylidene diaminoguanidines, when tested similarly also afforded merely unreacted hydrazone. When these brominations were attempted at 100° over 1–3 hr. periods, extensive decomposition of the hydrazones resulted.

(2) The corresponding reaction[7a] with tribenzylidene triaminoguanidine nitrate yielded initially an orange powder, m.p. 190° (yield 6.6 g. from 5 g. of hydrazone). When this powder was crystallized from either aqueous ethanol or acetic acid, it dehalogenated, the major product recovered being the original hydrazone. When a suspension of the orange powder in ethanol was treated with an excess of concentrated ammonia solution, a yellow solid, m.p. 198°, was obtained which proved to be merely the starting hydrazone free base.

Anal. Calcd. for $C_{22}H_{20}N_6$: C, 71.7; H, 5.4; N, 22.8. Found: C, 71.6; H, 5.0; N, 23.0.

When 1.0 g. of this orange powder was suspended in ethanol and treated with 0.56 ml. of phenylhydrazine, the light yellow transparent crystals which separated (0.6 g.), after further crystallization from ethanol, melted at 248° and corresponded to tribenzylidene triaminoguanidine hydrobromide.

Anal Calcd. for $C_{22}H_{21}N_6Br$: C, 58.8; H, 4.5; N, 18.7. Found: C, 59.4; H, 5.0; N, 18.6.

These two reactions demonstrate (a) that no ring halogenation occurred during the original bromination attempt, and (b) that the product isolated did not display the normal replacement reactions of ω-bromo halides.[4] Whether its physical properties and chemical reactions are due merely to loosely-bound, or even occluded, bromine, is not yet settled.

(3) Benzylidene guanylhydrazone was first benzoylated[7b] by the standard Schotten-Baumann technique.[8] The product, obtained in 90% yield, after recrystallization from aqueous ethanol melted at 164°.

Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71 4; H, 4.9; N, 15.1. Found: C, 71.5; H, 4.9; N, 15.5.

It was ascribed the structure (IIID) on the basis of previous data in the literature.[9] On bromination under the standard conditions a crude ω-bromo derivative (*sic.*), yield 83%, m.p. 261–267°, was obtained. This, on treatment with an excess of concentrated ammonium hydroxide solution, afforded the hydrazidine (IIIE) in 73% yield. After crystallization from ethanol this had a m.p. of 230°.

Anal. Calcd. for $C_{22}H_{19}N_5O_2$: C, 68.6; H, 4.9; N, 18.2. Found: C, 68.1; H, 4.7; N, 18.9.

The brominations of simpler guanylhydrazones has proven complex and is still under investigation.

(4) Bromination attempted under the above conditions at room temperature left benzylidene, furfurylidene, and 2,4-dinitrobenzylidene nitroaminoguanidines unaffected.[1,10] Under reflux conditions the hydrazones decomposed. When IIIC[1] was analogously refluxed for 8 hr. in acetic acid with 1 equivalent of bromine, a cream powder (in addition to unreacted, essentially insoluble hydrazone) was isolated. This crystallized from acetic acid as an ivory colored amorphous powder, m.p. > 360°. Its structure is still unknown.

Anal. Calcd. for $C_{11}H_{11}N_5Br_2O_2$: C, 32.2; H, 2.6; N, 20.0; Br, 38.2. Found: C, 32.3; H, 2.8; N, 19.2; Br, 38.1.

(*b*) *With benzylidene 5-hydrazinotetrazole* (*IA*). When IA, m.p. 235°, reported[11] m.p. 235°, was allowed to react under the general conditions of bromination at room temperature as detailed above it afforded IB in 72% yield. This crystallized from anhydrous chloroform as a white, amorphous powder, m.p. 176°.

Anal. Calcd. for $C_8H_7N_6Br$: C, 36.0; H, 2.6; N, 31.5; Br, 30.0. Found: C, 36.1; H, 2.9; N, 32.0; Br, 29.4.

When recrystallized from glacial acetic acid IB reverted to IA. In 50% aqueous ethanol, IB underwent further change and the new product was isolated as colorless, glistening blades, m.p. 188° (dec.).

Anal. Calcd. for $(C_8H_6N_6)_x$: C, 51.6; H, 3.2; N, 45.2. Found: C, 51.1; H, 3.2; N, 44.7.

By analogy with the observations of Chattaway *et al.*,[4] this product has been assigned, provisionally, the dihydro tetrazine structure (IIA). When reacted with excess bromine without further solvent IA formed apparently IC,*cf.* [4] which crystallized from glacial acetic acid as fine white needles, softening at 187° and melting at 190°.

Anal. Calcd. for $C_8H_6N_6Br_2.2H_2O$: C, 25.1; H, 2.6; N, 22.0; Br, 41.9. Found: C, 25.5; H, 2.8; N, 21.5; Br, 41.2.

When the 3-nitrophenyl analogue of IA, *viz.*, ID was allowed to react similarly, with bromine in acetic acid at room temperature but with a 3 day reaction period, the initial product then being crystallized from aqueous ethanol, it afforded, together with 70% unreacted hydrazone, the 3-nitrophenyl substituted tetrazine (IIB), in 20% yield. This crystallized as white needles, m p. 194°.

Anal. Calcd for $(C_8H_5N_7O_2)_x$: C, 41.6; H, 2.2; N, 42.4. Found: C, 41.8; H, 2.1; N, 42.0.

It should be reiterated that the presently adopted tetrazine formulations for IIA and IIB are merely based (a) on good microanalytical confirmation of the proposed structures and (b) by analogy with the behavior of related phenylhydrazones.[4] Additional structural evidence is being sought.

CHEMISTRY DEPARTMENT
UNIVERSITY COLLEGE
CORK, IRELAND
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
LOS ANGELES 24, CALIF.

(7) We are indebted for assistance with these reactions to (a) Dr. M. F. Cashman, M.S. and (b) Miss M. McGrath, M.S.

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., page 98, John Wiley and Sons, Inc., New York, N. Y., 1956.

(9) Compare W. G. Finnegan, R. A. Henry, and G. B. L. Smith, *J. Am. Chem. Soc.*, 74, 2981 (1952).

(10) This was not the case with the formaldehyde nitroguanylhydrazone. When, *e.g.*, a solution of 3 ml. of bromine in 30 ml. of acetic acid was added to the solid hydrazone at room temperature, a violent, explosive reaction occurred. Even at greater dilution, and at −4 to −10°, again very vigorous interaction with copious evolution of hydrogen bromide, was detected. Decomposition, and not ω-bromination, was the sole result encountered.

(11) Thiele and Marais, *loc. cit.*

Improved Synthesis of 4-Ethylpyridine

GODFREY WILBERT, LEO REICH, AND LEON E. TENENBAUM

Received November 9, 1956

The syntheses of 4-ethylpyridine[1–5] from pyri-

(1) J. F. Arens and J. P. Wibaut, *Rec. trav. chim.*, 61, 59 (1942).

(2) R. L. Frank and P. V. Smith, *Org. Syntheses*, 27, 38 (1947).

(3) T. Urbanski, Z. Biernacki, D. Gürne, L. Halski, M. Mioduszewska, B. Serafinowa, J. Urbanski and D. Zelazko, *Roczniki Chem.*, 27, 161 (1953); *Chem. Abstr.*, 48, 13688*b* (1954).

(4) T. Vitali and M. Sardella, *Chimica (Milan)*, 7, 229 (1952); *Chem. Abstr.*, 47, 6414*i* (1953).

(5) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, 60, 119 (1941).

dine, acetic anhydride, acetic acid, and zinc lead to low yields of 35–41% based on the pyridine charged. Because of the increased interest in 4-substituted pyridines, particularly derivatives of isonicotinic acid, an investigation was undertaken to develop an improved synthesis of 4-ethylpyridine.

Theoretically, one half of the charged pyridine is regenerated in the course of the reaction so the maximum yield of 4-ethylpyridine is only 50%.[6] In the present modified procedure the regenerated pyridine, in the reaction mixture, was subjected to further treatment in this same reaction mixture, was subjected to further treatment in this same reaction mixture, to increase the overall yield to 75%. Without using the regenerated pyridine, crude yields were increased from previously reported 35.5–41% to 48–50%. By using the regenerated pyridine, in what is referred to as the cyclic process, crude yields up to 78% were obtained. Yields of over 80% were obtained, based upon recovered pyridine. Less expensive iron powder (Belmont 98%) was substituted for activated zinc.[7] (It was found that regular zinc powder gave yields similar to those obtained employing activated zinc). Iron filings and impure iron powder resulted in lower yields compared to pure powder. It was also determined that the violent exothermic reactions that occurred during certain stages of the original procedure were more readily controlled by running the reaction at higher temperatures and adding the iron at about 80–100° C. instead of 35–40° C. Water was used to replace acetic acid at one stage of the reaction, and benzene was substituted for chloroform in the extraction of the product.

A study of the influence of the initial concentration of acetic acid was also made. The experimental results indicated that this is important, and in the cyclic process a large initial quantity of the acid has an adverse effect, probably because the unreacted acid competes with acetic anhydride by forming a salt with pyridine in the second phase of the process.

Where the maximum theoretical yield of 4-ethylpyridine is 50%, the process is referred to as phase and where the regenerated pyridine is further treated, without prior separation from the reaction mixture, the process is referred to as cyclic.

EXPERIMENTAL

Phase process (optimum conditions). To 200 g. of pyridine, in a flask equipped with a thermometer, a $^1/_{15}$ h.p. motor and a sealed stainless steel stirrer, was added 600 ml. of acetic anhydride. The temperature was raised to 80° C., and 165 g. of iron powder (Belmont Grade 98.5%) was added, in portions, over a 1-hr. period, maintaining the same temperature. Over a 0.5-hr. period 30 ml. of water was added and the temperature was not permitted to exceed 97° C. The mixture was cooled to 90° C. and 103 g. of iron powder was added, in portions, over a 0.5-hr. period, the temperature being maintained between 80–90° C. The temperature of the reaction mixture was raised to 136° C. over a 0.5-hr. period and reflux maintained for 1.5 hr. With provisions for cooling, 500 ml. of water was slowly and carefully added, not permitting the temperature to exceed 110° C. After the water was added, the *p*H of the mixture was adjusted to 9.5–10 with 50% caustic and then steam distilled. The oily layer of the steam distillate was separated and the lower aqueous phase was saturated with potassium carbonate and then extracted with three 175 ml. portions of benzene. The benzene extracts were combined with the oily layer, dried over anhydrous potassium carbonate, and fractionated at atmospheric pressure. The fraction, b.p. 145–167° C., n_D^{23} 1.500 was collected, 131.0 g. (49.5%). Redistillation of the product gave 120.3 g., b.p. 160–167° C., yield, 45.5%. By titration of the lower boiling fractions with standard alkali, 92 g. as pyridine was accounted for.

Cyclic process. From a series of 12 runs, the following procedure was found to give optimum yields. Employing the same apparatus, as previously described for the phase process, 100 g. of pyridine and 300 ml. of acetic anhydride were heated to 80° C. and 84 g. of iron powder was gradually added over a 0.5-hr. period. The temperature was maintained at 80° C. for 1.5 hr., 30 ml. of acetic acid was added followed by the gradual addition of 42 g. of iron powder over 0.5-hr. Then 150 ml. of acetic anhydride was added and the temperature raised to 137° C. and maintained there for 1 hr. An additional 100 ml. of acetic anhydride was then added, permitting the temperature to fall to 127° C. Over the next 0.5-hr., 50 g. of iron powder was gradually added and the temperature rose to 136° C. The very viscous reaction mixture was stirred vigorously for 0.5 hr. and 60 ml. of acetic acid were added, producing a more fluid reaction mixture. At 136° C., a fourth gradual addition of 25 g. of iron powder was made over a 0.5-hr. period, and reflux maintained for 0.5 to 1 hr. Water and 50% caustic were then carefully added, permitting the temperature to remain above 100° C., while applying cooling. The reaction mixture was then treated as previously described. The crude yield was 102 g. of product, b.p. 145–170° C., n_D^{23} 1.500 (78%). Four grams of product boiling above 170° C. were also obtained, n_D^{23} 1.499. Fractionation of the crude resulted in a product, b.p. 160–167° C., n_D^{23} 1.500, neutralization equivalent 109, yield 70.5% of theory.

HARRIMAN AND YONKERS LABORATORIES
NEPERA CHEMICAL CO., INC.
YONKERS 2, N. Y.

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Derivatives of (1-Aminocyclohexyl)methanol

WAYLAND E. NOLAND, JAMES F. KNELLER,[1] AND DAVID E. RICE[1]

Received November 26, 1956

Nitrocyclohexane undergoes base-catalyzed condensations with formaldehyde to give (1-nitro-

(1) University of Minnesota Graduate School research assistants, summer 1956. We are indebted to the Graduate School of the University of Minnesota for a grant in support of this research.

cyclohexyl)methanol (I) in 93% yield,[2,3] and with acetaldehyde to give 1-(1-nitrocyclohexyl)ethanol in unstated yield.[4] High pressure catalytic hydrogenation of I gives (1-aminocyclohexyl)methanol (II) in 43[3]–80[2]% yield. High pressure hydrogenation is unnecessary, however, since we have obtained II in 50–60% yield by hydrogenation of I over a Raney nickel catalyst at an initial pressure of 2 atm. in methanol, absolute ethanol, or 1,4-dioxane solutions, or without solvent. II was first prepared, in excellent yield,[5] from cyclohexanone through a Strecker synthesis,[6] followed by high-pressure catalytic hydrogenation of the ethyl ester of the α-aminoacid.

The amino alcohol II yielded dibenzoyl and diacetyl derivatives having both ester and amide groups, as shown by the presence in their infrared spectra of both ester and amide (amide I) carbonyl bands and NH stretching and amide NH deformation (amide II) bands. Refluxing of the diacetyl derivative with ethanol in the presence of sulfuric acid removed an acetyl group, yielding the acetamide of II.[7] The corresponding formamide of II was obtained by refluxing II with formic acid. That the formamide and acetamide of II are amide-alcohols and not amino-esters is shown by their neutrality and by the presence in their infrared spectra of amide I and II bands and the absence of ester carbonyl bands.

The 2-oxazolidone (III) of the amino alcohol II has previously been obtained in 89% yield by heating II with diethyl carbonate in the presence of sodium methoxide.[2] We have also obtained III in 34% yield by heating II with urea at 185° without a catalyst. It was hoped that II could likewise be converted to the heterocyclic spiranes IV and V. Precedent exists for the formation from ethanolamines and acetic acid of 2-oxazolines[8] containing the heterocyclic ring of IV (see Fig. 1). Models indicate, however, that the presence of unsaturation in the 2-oxazoline ring of the 5-6 spirane IV would impose a very considerable strain. Compound IV was not obtained. Refluxing of II with excess diethyl oxalate also did not yield the saturated heterocyclic 6-6 spirane V (see Fig. 1), but rather the oxamide of II, indicating that in this case the preferred reaction course is *intermolecular* amine-ester interchange. That this oxalyl derivative is the diamide and not the diester with free amino groups is shown by its neutrality and by the presence in its infrared spectra of amide I and II bands and the absence of the ester carbonyl-band. The formation of the oxamide of II is consistent with the fact that the normal products of ester-ethanolamine reactions, isolated without acid treatment, are the corresponding ethanolamides.[9]

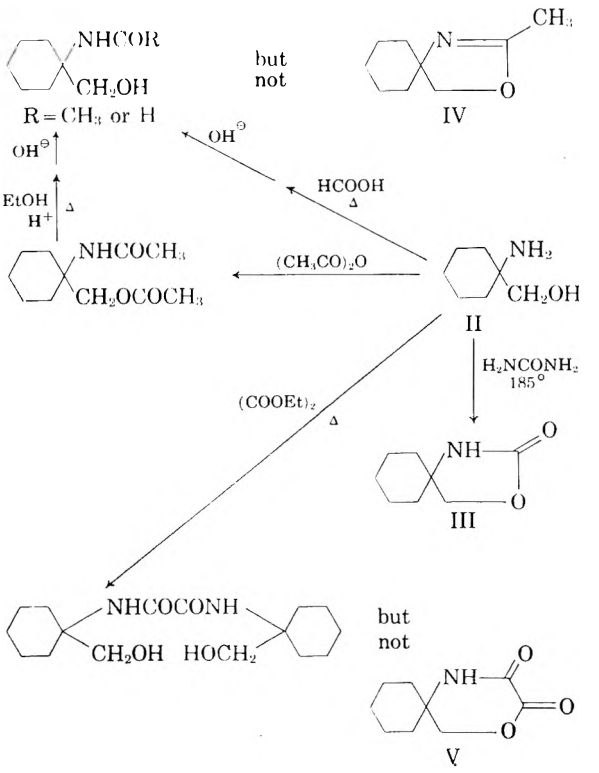

FIG. 1. SOME REACTIONS OF (1-AMINOCYCLOHEXYL)METHANOL (II)

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

(1-Nitrocyclohexyl)methanol (I). The compound was obtained in about 80% yield by a modification of the method of Newman and Edwards[2] in which 20% methanolic potassium hydroxide (50 cc.) was added slowly, with occasional shaking, to a mixture of nitrocyclohexane[10] (1 mole) and paraformaldehyde (1 mole of CH_2O) containing 250 cc. of methanol to moderate the reaction. After the paraformaldehyde had dissolved slowly as the temperature rose to 52°, the solution was refluxed for 1 hr. and let stand overnight. Our analytical sample had the following properties: n_D^{25} 1.4845; ν_{OH} (cm.$^{-1}$) 3390, ν_{NO_2} 1542, 1352; m.p. ~ 0–4°; b.p. 136–137° (5.5 mm.). Reported:[2] n_D^{20} 1.4853; b.p. 113–114° (3 mm.).

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.91; H, 8.46; N, 9.00.

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(3) W. B. Wheatley, *J. Am. Chem. Soc.*, **76**, 2832 (1954).

(4) A. G. Susie (to Purdue Research Foundation), U. S. Patent 2,281,253, April 28, 1942.

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(7) A referee has kindly pointed out that the acid hydrolysis of the diacetyl derivative of II probably yielded a salt of the aminoacetate of II, which then rearranged under the alkaline conditions of the workup procedure to the acetamide of II. Such rearrangements are normal for ethanolamines: A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 200 (1947).

(8) S. H. Shapiro, "Nitroparaffin Symposium," Commercial Solvents Corp., New York, N. Y., 1956, p. 21.

(9) See reference in note 7.

(10) We are grateful to the E. I. du Pont de Nemours & Co., Inc., Explosives Department, for a one-gallon sample of nitrocyclohexane.

(1-Nitrocyclohexyl)methyl 3,5-dinitrobenzoate (3,5-dinitrobenzoate of I). From benzene–light petroleum (b.p. 60–68°), white platelets, m.p. 131–132.5°. $\nu_{C=O}$ (cm.$^{-1}$) 1733 in Nujol, 1742 in CS_2; ν_{NO_2} 1545, 1347 in Nujol, 1339 in CS_2.

Anal. Calcd. for $C_{14}H_{15}N_3O_8$: C, 47.59; H, 4.28; N, 11.90. Found: C, 47.49 H, 4.19; N, 12.06.

(1-Aminocyclohexyl)methanol (II). (1-Nitrocyclohexyl)-methanol was hydrogenated in methanol with Raney nickel catalyst at an initial pressure of 2 atm. at room temperature in a Parr low pressure hydrogenation apparatus, causing the mixture to become quite warm. After removal of the catalyst and solvent, the crude product was taken up in ether and extracted with dilute hydrochloric acid. The acid extract was washed with ether, strongly basified with concentrated potassium hydroxide solution, salted out with sodium chloride, and extracted repeatedly with ether. Drying and evaporation of the ether extracts, followed by vacuum distillation of the residue, gave colorless, syrupy (1-aminocyclohexyl)methanol (60% yield), having a potent sperm-like odor. Our analytical sample had the following properties: n_D^{25} 1.4959; ν_{OH} (cm.$^{-1}$) ~3260 (broad), ν_{NH} 1589; m.p. ~37–39.5° (but readily supercools); b.p. 84° (1 mm.). Reported: n_D^{20} 1.4970,[6] 1.4964[3]; b.p. 117–118° (27 mm.),[6] 114–118° (14 mm.),[3] 111–114° (13 mm.).[2]

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.99; H, 11.45; N, 10.85.

(1-Aminocyclohexyl)methanol hydrochloride (hydrochloride of II).[11] From chloroform-petroleum (b.p. 90–100°), white crystals, m.p. 161.5–163.5°. Reported:[5] m.p. 158–159°, but no analyses were given.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.75; H, 9.74; N, 8.46. Found: C, 51.05; H, 9.71; N, 8.43.

(1-Aminocyclohexyl)methanol sulfate (sulfate of II). White needles, m.p. 237.5–240.5°, from ethanol.

Anal. Calcd. for $C_{14}H_{32}N_2O_6S$: C, 47.17; H, 9.05; N, 7.86. Found: C, 46.71; H, 9.01; N, 8.08. Qualitative analysis showed sulfur to be present.

(1-Benzamidocyclohexyl)methyl benzoate (dibenzoyl derivative of II). The compound was prepared by the Schotten-Baumann reaction. From methylene chloride–light petroleum (b.p. 60–68°), white featherlets, m.p. 100–102°. ν_{NH} (cm.$^{-1}$) 3350, 1537 in Nujol, 3420 in CS_2; $\nu_{C=O}$ 1720, 1643 in Nujol, 1719, 1671 in CS_2.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.76; H, 6.81; N, 4.16.

(1-Acetamidocyclohexyl)methyl acetate (diacetyl derivative of II). The ester was obtained by warming (1-aminocyclohexyl)methanol with acetic anhydride on the steam bath for 4.5 hr. From methylene chloride-light petroleum (b.p. 60–68°), thick, white needles, m.p. 63–66.5°. ν_{NH} (cm.$^{-1}$) 3290, 3190, 1552 in Nujol solution, 3410, 3300 in CS_2, 3410, 3310 in $CHCl_3$; $\nu_{C=O}$ 1745, 1644 in Nujol solution, 1736, 1654 in CS_2, 1725, 1651 in $CHCl_3$.

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.21; H, 8.98; N, 6.58.

(1-Acetamidocyclohexyl)methanol (acetamide of II). A solution of (1-acetamidocyclohexyl)methyl acetate (1.00 g., 0.00469 mole) and concentrated sulfuric acid (0.25 cc.) in 95% ethanol (15 cc.) was refluxed for 2.5 hr. After distillation of the ethanol, the residue was made slightly basic with sodium bicarbonate solution and extracted repeatedly with ether. Evaporation of the ether extracts, solution of the residual oil in methylene chloride and light petroleum (b.p. 60–68°), concentration, and cooling in an ice bath caused precipitation of small white needles (0.23 g., 0.00134 mole, 29%). Several recrystallizations from methylene chloride-light petroleum gave small white needles of (1-acetamidocyclohexyl)methanol, m.p. 121–123°. ν_{NH} (cm.$^{-1}$) 3300, 1548 in Nujol, 3430, 3310 in $CHCl_3$; $\nu_{C=O}$ 1646 in Nujol, 1653 in $CHCl_3$.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 63.16; H, 9.97; N, 8.15.

(11) Prepared by James H. Cooley.

(1-Formamidocyclohexyl)methanol (formamide of II). (1-Aminocyclohexyl)methanol (3.9 g., 0.030 mole) and anhydrous formic acid (10 cc., 0.26 mole) were refluxed for 4 hr. When the reactants were mixed, considerable heat was evolved and a white precipitate formed, probably the formic acid salt, but this dissolved as the reactants were warmed to reflux. The cooled solution was poured into water (30 cc.), neutralized, and saturated with solid sodium carbonate and allowed to evaporate to dryness at room temperature. The crystalline residue was extracted repeatedly with methylene chloride. Evaporation of the methylene chloride and recrystallization from methylene chloride-light petroleum (b.p. 60–68°) gave white crystals (1.01 g., 0.0064 mole, 21%). Three more recrystallizations yielded dense, granular white crystals of (1-formamidocyclohexyl)methanol (0.73 g., 0.0046 mole, 15%), m.p. 124–125.5°. ν_{NH} (cm.$^{-1}$) 1548 in Nujol, 3400 in $CHCl_3$; ν_{OH} ~3180 (broad) in Nujol; $\nu_{C=O}$ 1659 in Nujol, 1674 in $CHCl_3$.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.13; H, 9.73; N, 8.94.

3-Oxa-1-azaspiro[4,5]decan-2-one (III) *(2-oxazolidone of II).* The compound was obtained in 34% yield by heating (1-aminocyclohexyl)methanol with a 100% molar excess of urea at 185° for 1 hr. without catalyst. From methylene chloride-light petroleum, white, chunky crystals, m.p. 82–84.5°. ν_{NH} (cm.$^{-1}$) 3210, 1544 in Nujol, 3240 in CCl_4; $\nu_{C=O}$ 1748 in Nujol and in CCl_4. Reported:[2] m.p. 81–82°.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.22; H, 8.26; N, 9.01.

N,N'-Bis(1-hydroxymethylcyclohexyl)oxamide (oxamide of II). (1-Aminocyclohexyl)methanol (4.4 g., 0.034 mole), diethyl oxalate (9.9 g., 0.068 mole), and 1,4-dioxane (125 cc.) were refluxed for 15 hr. The mixture was poured into water, causing the precipitate to dissolve, giving an acidic solution. The solution was made slightly basic with sodium bicarbonate and extracted several times with ether. The ether extracts were dried, distilled, and the residual dioxane solution was evaporated on the steam bath in a current of air, leaving a brown oil, which crystallized on standing. Four recrystallizations, one with charcoal, from methylene chloride-light petroleum (b.p. 60–68°) yielded white platelets of *N,N'*-bis(1-hydroxymethylcyclohexyl)oxamide (0.75 g., 0.0024 mole, 14%), m.p. 174.5–176.5°. ν_{NH} (cm.$^{-1}$) 3420, 3350, 1518 in Nujol, 3370, 1516 in $CHCl_3$; γ_{O-O} 1664 in Nujol, 1672 in $CHCl_3$.

Anal. Calcd. for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.46; H, 8.82; N, 8.92.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.

Urea Complexes of Some Higher Methylalkanes

ROBERT W. SCHIESSLER[1] AND DAVID D. NEISWENDER, JR

Received November 26, 1956

The principal requirement for the formation of crystalline channel inclusion complexes by urea and a hydrocarbon is the presence of a sufficiently long normal carbon chain in the hydrocarbon molecule. While studying the requirement for the for-

(1) Present address, Research & Development Laboratory, Socony Mobil Oil Co., Paulsboro, N. J.

mation of such complexes, Schiessler and Flitter[2] found that *n*-tridecane yields a crystalline complex while 7-methyltridecane does not. The inhibiting effect of the methyl group prompted further research.

The purpose of this investigation was to define the length of the smallest straight carbon chain which will allow complex formation of 2-methylalkanes and to determine whether hydrocarbons with a central methyl branch will form complexes if the straight carbon chain is sufficiently long. The reactions between a saturated solution of urea in methanol and the following five hydrocarbons were studied: 2-methyldecane, 2-methylpentadecane, 2-methylheptadecane, 2-methyltricosane and 10-methyleicosane.

In the 2-methylalkane series the amount of complex formed, as well as the rate of formation of the complex, increased as the length of the straight carbon chain was increased. 2-Methyldecane yielded only a trace of crystalline complex, while 2-methyltricosane was precipitated almost quantitatively. These results indicate the borderline for the formation of insoluble complexes of urea and 2-methylalkanes at 25° C. probably falls just below 2-methyldecane. The studies of Redlich and co-workers,[3] employing hydrocarbon mixtures, suggest that 2-methylalkanes below 2-methyldodecane will not form stable urea complexes at 25° C.

10-Methyleicosane produced a crystalline complex in a yield of about 22%, showing that the inhibitive effect of a centrally located methyl group can be overcome if the straight chain is sufficiently long. Analysis of the complex gave 16.3 molecules of urea per molecule of 10-methyleicosane. Redlich and co-workers[3] formulated the following equation for the composition of urea complexes of the normal alkanes:

$$m = 0.653n + 1.51$$

where m = number of urea molecules,
n = number of carbon atoms

From a study of the crystalline structure of urea complexes, Smith[4] obtained the equation: $m = 0.6925n + 1.49$. Using all 21 carbon atoms of 10-methyleicosane, the calculated values of m are 15.2 and 16.0, respectively. Since the experimental value, 16.3, is slightly higher, it would seem that all the carbon atoms, including the methyl group, are involved in the inter-action with the expanded urea lattice.

None of the five hydrocarbons formed a complex with thiourea.

(2) R. W. Schiessler and D. Flitter, *J. Am. Chem. Soc.*, **74**, 1720 (1952).

(3) O. Redlich, C. M. Gable, A. K. Dunlop, and R. W. Millar, *J. Am. Chem. Soc.*, **72**, 4153 (1950).

(4) A. E. Smith, *J. Chem. Phys.*, **18**, 150 (1950).

EXPERIMENTAL

Reagents. C. P. urea and thiourea, Coleman and Bell, Norwood, Ohio. Methanol, commercial synthetic. Methyl ethyl ketone, technical, Shell Chemical. Hydrocarbons, synthesized[5] by the authors and others at this laboratory.

Procedure. A 10 ml. sample of the hydrocarbon and 100 ml. of a saturated solution of urea in methanol were placed in a large ampoule. The ampoule was sealed and shaken mechanically. Shaking time was 2.5 days except in the case of 2-methyldecane where 4 days of shaking were necessary for complex formation. The ampoule was then opened and the solid complex collected on a sintered glass funnel. The complex was washed with urea-methanol solution, and then with methylcyclohexane to remove any adhering hydrocarbon. The crystalline material was air dried and decomposed with a very small amount of hot water. The formation of an oily hydrocarbon layer confirmed the presence of a complex.

The procedure for testing with thiourea was identical to that above, except that 3 drops of methylethyl ketone were added to each ampoule to aid complex formation. All the tests were run at 25° C.

The urea complex of 10-methyleicosane was analyzed by decomposing 4.411 g. with hot water. The hydrocarbon was extracted with 4 portions of hexane. Evaporation of the hexane yielded 1.026 g. of hydrocarbon. This composition corresponds to 16.3 molecules of urea per molecule of 10-methyleicosane.

Acknowledgment. The authors express their appreciation to the American Petroleum Institute for the grant which made this research possible.

AMERICAN PETROLEUM INSTITUTE RESEARCH PROJECT 42
WHITMORE LABORATORY, DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PA.

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Reactions of the Perfluoronitriles. II. Syntheses of 2,4,6-*tris*(Perfluoroalkyl)-1,3,5-Triazines[1,2]

WILLIAM L. REILLY AND HENRY C. BROWN

Received November 29, 1956

McBee, Pierce, and Bolt[3] have reported a synthesis of 2,4,6-*tris*(trifluoromethyl)-1,3,5-triazine by trimerization under pressure of trichloroacetonitrile in the presence of a strong acid, hydrogen

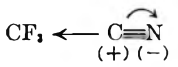
(1) This work was supported by the Office of Naval Research under contract Nonr-580(03); NR 356-333 with the University of Florida and is taken in part from the dissertation presented by William L. Reilly to the Graduate School of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) Presented at the Fluorine Symposium, 126th Meeting. AMERICAN CHEMICAL SOCIETY, Minneapolis, Minn., September, 1955.

(3) E. T. McBee, O. R. Pierce, and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 391 (1947).

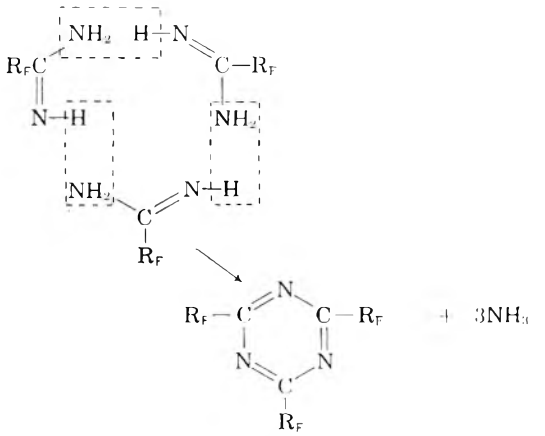
chloride, and subsequent fluorination of the cyclic product by hydrogen fluoride and antimony pentachloride. This method of preparation was improved somewhat by Norton[4] by the use of aluminum chloride with hydrogen chloride to promote the initial polymerization of trichloroacetonitrile.

This paper describes the formation of *s*-triazines from perfluoroalkyl nitriles. In this reaction no acid catalyst is necessary and therefore the perfluoronitrile molecule may be considered activated by the inductive effect of the fluorocarbon group and to exist predominantly in the state represented by:



Trifluoroacetonitrile, pentafluoropropionitrile and heptafluorobutyronitrile have been trimerized under heat and pressure to produce the 2,4,6-*tris*(perfluoroalkyl)-1,3,5-triazines. The minimum pressure for this reaction is 700–900 p.s.i. and the optimum temperature between 300° and 350°. Under these conditions, the reaction time is between 30 and 120 hr., depending on the nitrile used. Trimerization of trifluoroacetonitrile is considerably more rapid than that of the nitriles with longer perfluoroalkyl chains, but the yield of triazine based on unrecovered starting material is in the range of 45 to 60% for each of the nitriles studied. The conversion range (based on starting material) is generally higher for trifluoroacetonitrile (approximately 30%) than for heptafluorobutyronitrile (from 8 to 10%).

The 2,4,6-*tris*(perfluoropropyl)-1,3,5-triazine and the 2,4,6-*tris*(perfluoroethyl)-1,3,5-triazine were prepared also by condensation reactions of heptafluorobutyramidine and of pentafluoropropionamide involving cyclization and elimination of ammonia,



where R_F represents C_3F_7 or C_2F_5. Preparation of the triazines by this method begins with preparation of the amidine from the nitrile and liquid ammonia.[5] The amidines are heated in a glass flask above their melting point and the course of the reaction followed by the evolution of ammonia.

Although the perfluoronitriles are starting points in both of the above methods of preparing the perfluoroalkyl-substituted *s*-triazines, the method proceeding through the amidine involves no high pressure apparatus and is carried out at lower temperatures and is therefore somewhat more convenient if pressure equipment is not available.

The 2,4,6-*tris*(perfluoroalkyl)-1,3,5-triazines are neutral, colorless liquids. As has been noted previously,[3] they produce a burning sensation in the respiratory tract when inhaled. They may be hydrolyzed by aqueous base to form the alkali metal salt of the fluorocarbon acid or they may undergo alcoholysis to form the ester of the fluorocarbon acid. They are not attacked by concentrated acid. A sample of 2,4,6-*tris*(pentafluoropropyl)-1,3,5-triazine was sealed in a glass tube with concentrated sulfuric acid and heated at 300° for 72 hr. with no detectable change.

Infrared absorption spectra of each of the perfluoroalkyl-substituted *s*-triazines prepared shows a characteristic strong band at 1565 cm.$^{-1}$ (6.4 μ). This is probably characteristic of the —C=N— in these conjugated cyclic compounds since studies of organic compounds of similar structure have placed the —C=N— absorption in the 1580–1520 cm.$^{-1}$ range.[6]

EXPERIMENTAL

Trifluoroacetonitrile, pentafluoropropionitrile and heptafluorobutyronitrile. These compounds were prepared by dehydration of the perfluoroamides as described by Swarts[7] and by Gilman and Jones.[8]

Pentafluoropropionamidine and heptafluorobutyramidine. These compounds were prepared by reaction of the perfluoronitriles with liquid ammonia.[5]

Cyclization of perfluoroalkyl nitriles. All trimerizations of the perfluoroalkyl nitriles were carried out in a stainless steel pressure vessel of 300-ml. capacity. The nitriles were condensed in the previously evacuated reaction vessel by transfer through a vacuum system line. Temperature of the reactions was controlled automatically. The products were fractionated in a column of 9 theoretical plates packed with glass helices.

(*a*) *2,4,6-tris(Trifluoromethyl)-1,3,5-triazine.* Trifluoroacetonitrile (55 g., 0.58 mole) was placed in the stainless steel reaction vessel as described above and heated to 300°. Pressure in the reaction vessel rose to 1000 p.s.i., then decreased over 16 hr. heating at 300° to 600 p.s.i. Little decrease in pressure was shown during the last 5 hr. After cooling to room temperature, the reaction vessel was opened and 22 g. (0.23 mole) of unreacted trifluoroacetonitrile collected in a Dry-Ice-cooled trap. The high boiling material, 16 g., was poured from the vessel and refractionated to give 14 g. of 2,4,6-*tris*(trifluoromethyl)-1,3,5-triazine, b.p.,

(4) T. R. Norton, *J. Am. Chem. Soc.*, 72, 3527 (1950).

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95.0–96.0°; n_D^{25}, 1.3161; d^{25}, 1.593; mol. wt., calcd. 285, found 288 (Victor Meyer vapor density). Reported[3] b.p., 98.3–98.5°; n_D^{25}, 1.3231; d^{26}, 1.5857.

(*b*) *2,4,6-tris(Pentafluoroethyl)-1,3,5-triazine.* Pentafluoropropionitrile (65 g., 0.45 mole) was condensed in the stainless steel reaction vessel and heated at 300° for 120 hr. The reaction vessel was then cooled, 27 g. of unreacted pentafluoropropionitrile recovered and 38 g. of higher boiling material poured from the vessel. Fractionation of this higher boiling portion gave 2,4,6-*tris*(pentafluoropropyl)-1,3,5-triazine, b.p., 121–122°, n_D^{26}, 1.3131, d^{25}, 1.651.

Anal. Calcd. for $C_9H_{15}N_3$: mol. wt., 435; N, 9.65; sapon. equiv., 435. Found: mol. wt., 431; N, 8.99; sapon. equiv., 431.

(*c*) *2,4,6-tris(Heptafluoropropyl)-1,3,5-triazine.* Heptafluorobutyronitrile (195 g., 1.0 mole) was condensed in a 300-ml. capacity stainless steel reaction vessel and heated to 350°. Initial pressure at 350° was 1879 p.s.i.; pressure decreased to 1670 p.s.i. after 114 hr. At this time the temperature was raised to 400° and the consequent pressure to 1980 p.s.i. No further decrease in pressure was found during the 16-hr. period at 400°. The reaction vessel was cooled to room temperature and 168 g. of unreacted heptafluorobutyronitrile recovered. The remaining higher boiling material (20 g.) was poured from the reaction vessel and fractionated to give 15 g. of 2,4,6-*tris*(heptafluoropropyl)-1,3,5-triazine, b.p., 164.5–165.0°; n_D^{25}, 1.3095, d^{25}, 1.716.

Anal. Calcd. for $C_{12}F_{21}N_3$: sapon. equiv., 585; N, 7.18. Found: sapon. equiv., 576; N, 6.96.

Deammoniation and cyclization of perfluoroalkyl amidines

(*a*) *2,4,6-tris(pentafluoroethyl)-1,3,5-triazine.* Pentafluoropropionamidine (55 g., 0.34 mole) was placed in a round-bottom flask equipped with a reflux condenser and heated in an oil bath at 125° for 3 hr. After this time, the evolution of ammonia was essentially complete. The remaining liquid was fractionated to give 17 g. of 2,4,6-*tris*(pentafluoroethyl)-1,3,5-triazine, colorless liquid, b.p., 122°; n_D^{25}, 1.3135; d^{25}, 1.6504; yield, 35%.

(*b*) *2,4,6-tris(Heptafluoropropyl)-1,3,5-triazine.* Heptafluorobutyramidine (36 g., 0.185 mole) was heated in a round-bottom flask equipped with a reflux condenser by an oil bath at 150° for 4 hr. Fractionation of the resulting liquid gave 23 g. of 2,4,6-*tris*(heptafluoropropyl)-1,3,5-triazine, b.p. 165°, n_D^{25}, 1.3095; yield 64%.

Department of Chemical Engineering and
Department of Chemistry
University of Florida
Gainesville, Fla.

Preparation of Some *p*-Phenylazobenzoyl Peptides

J. H. Loudfoot and V. Laxdal

Received November 30, 1956

In the course of other studies in this laboratory we have had occasion to prepare the *p*-phenylazobenzoyl derivatives of four dipeptides, type formula $C_6H_5—N{=}N—C_6H_4CONHCHRCONHCHR'COOH$. As they have not been previously reported, we wish to report the preparation. The dipeptides (glycylglycine, glycyl-DL-alanine, DL-alanylglycine, and DL-alanyl-DL-alanine) were prepared by the method of Sheehan and Frank.[1] The condensation with *p*-phenylazobenzoyl chloride was essentially an extension of the procedure which Karrer, Keller, and Szönyi[2] used in preparing *p*-phenylazobenzoyl amino acids by the Schotten-Baumann reaction.

EXPERIMENTAL

General procedure. A solution of 0.489 g. (0.002 mole) *p*-phenylazobenzoyl chloride in 40 ml. ether was added slowly to a stirred aqueous solution made from 0.002 mole dipeptide and 0.002 mole sodium hydroxide, at 0–5°, and the mixture stirred 1.5 hr. at 0–5°. A further 0.002 mole of alkali in aqueous solution was added in small amounts over 3 hr. and stirring at 0–5° continued a further 3 hr. after completing the addition.

Acidification with dilute hydrochloric acid precipitated the product as an orange solid which was filtered and dried. The solid was heated under reflux with petroleum ether (30–60°) to extract any unconverted acid chloride, then with benzene to extract any *p*-phenylazobenzoic acid. The residue was then recrystallized from ethanol to constant melting point.

Mixed melting point determinations of product with *p*-phenylazobenzoic acid and with the appropriate amino acid derivatives in turn showed that it was none of these.

Further very small amounts of peptide derivative could be obtained by separating the ether layer from the acid filtrate, evaporating to dryness from a water bath, heating the small quantity of residual solid successively with petroleum ether and benzene, and recrystallizing from ethanol. Identity with main product was confirmed by mixed melting point determination.

This general procedure was used to prepare all four derivatives. An alternative procedure, differing only in detail, was used for preparing *p*-phenylazobenzoyl glycylglycine, but was not used for the other derivatives.

Alternative procedure. The acid chloride (4.89 gm. or 0.02 mole, in 40 ml. ether) was added at 0–5° over 0.5 hr. to an aqueous solution made from 2.64 g. glycylglycine (0.02 mole) and 0.04 mole sodium hydroxide, and agitation continued 3 hr. at 0–5°. The ether layer was separated from the aqueous layer, washed three times with 0.02*N* NaOH, and the washings added to the main aqueous layer. Acidification of the aqueous solution with dilute hydrochloric acid precipitated the product, which was isolated and purified as described in the general procedure.

p-Phenylazobenzoyl glycylglycine. A yield of 0.56 g. (82.3%), m.p. 236–237° (corr.) was obtained by the general procedure.

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: N, 16.46. Found: N, 16.22.

Using the alternative procedure, 5.5 g. product (80.9%), m.p. 236° (corr.) was obtained, identical with that from the general procedure.

p-Phenylazobenzoyl glycyl-DL-alanine. The yield was 0.4 g. (60%), m.p. 236.5–237.5°.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: N, 15.81. Found: N, 15.70.

p-Phenylazobenzoyl DL-alanylglycine. The yield was 0.5 g. (71%), m.p. 224.5–225.5°.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: N, 15.81. Found: N, 15.67.

p-Phenylazobenzoyl DL-alanyl-DL-alanine. The yield was 0.56 g. (76%), m.p. 233–234°.

Anal. Calcd. for $C_{19}H_{20}N_4O_4$: N, 15.21. Found: N, 15.05.

Acknowledgment. The purchase of chemicals and equipment was made possible by grants from the National Research Council of Canada.

Department of Chemistry
University of Manitoba
Winnipeg, Manitoba
Canada

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Addition of Alkyl Orthoformates to Olefin Oxides[1]

O. C. Dermer and Frank Bier Slezak[2]

Received December 6, 1956

Alkyl orthoformates react with olefin oxides in the presence of boron trifluoride to give compounds of the type $HC(A_xOR)(A_yOR)(A_zOR)$, in which A is an olefin oxide unit and x, y, and z are any integers including zero. If the concentration of boron trifluoride exceeds 0.5% or the temperature 10°, the alkyl orthoformate is mostly degraded to the alkyl formate and the dialkyl ether. Concentrated sulfuric acid, anhydrous stannic chloride, hydrated calcium silicate, and boron trifluoride ethereate do not catalyze the reaction. Heating the reagents without catalyst in sealed tubes caused no change at 110–135° and explosion at 145–147°. As might be expected, the 1:1 addition was favored by keeping the orthoformate in excess. The principal differences between this reaction and the addition of acetals to olefin oxides[3] are (a) the tolerance of higher catalyst concentration by the acetals, and (b) the adjacency of olefin oxide units in the acetal adducts, *e.g.*, $CH_3O(CH_2CH_2O)_2CH_2OCH_3$, but predominant nonadjacency in the orthoester adducts, such as $HC(OCH_2CH_2OC_2H_5)_3$.

EXPERIMENTAL

Ethyl orthoformate and ethylene oxide. Boron trifluoride (1.5 g., 0.02 mole) was dissolved in ethyl orthoformate (300 g., 2 moles) at 0° contained in a one-liter, three-neck flask equipped with an ice water-cooled reflux condenser, a power stirrer, and a thermometer. A solution of ethylene oxide (22 g., 0.5 mole) in chilled ethyl orthoformate (150 g., 1 mole) was added to the catalyst solution at such a rate as to maintain the temperature between 3 and 6°. After 5 hr. more at 0–5° the boron trifluoride was destroyed by stirring the mixture for 30 min. with potassium carbonate (25 g.) dissolved in about 30 ml. of water. Anhydrous sodium sulfate (50 g.) was stirred in during 15 min., and the mixture was allowed to warm to room temperature overnight. The solids were filtered off and washed with ethyl ether and the ether washings combined with the filtrate. The mixture was distilled at atmospheric pressure to remove the ethyl ether, degradation products of ethyl orthoformate, and finally the excess ethyl orthoformate. The residue was distilled at reduced pressure through a Todd column to separate the products, which appeared in three principal fractions.

1-Diethoxymethoxy-2-ethoxyethane (*I*), b.p. 112–117° (35 mm.), n_D^{20} 1.4060, d_{20} 0.9254, yield 45 g. (47%).

Anal. Calcd. for $C_9H_{20}O_4$: C, 56.22; H, 10.49; MR, 50.4. Found: C, 56.40; H, 10.51; MR, 51.0.

I was characterized by hydrolysis in 6*N* hydrochloric acid to (a) ethanol, yielding its 3,5-dinitrobenzoate, m.p. 92°, and (b) 2-ethoxyethanol, also identified as the 3,5-dinitrobenzoate, m.p. 67–69°.[4]

1-Diethoxymethoxy-2-(2-ethoxyethoxy)ethane (*II*) *and ethoxy-bis-(2-ethoxyethoxy)methane* (*III*) were obtained as a mixture boiling at 156–158° (35 mm.) in 17% yield (10 g.). The mixture had n_D^{20} 1.4190 and d_{20} 0.9824.

Anal. Calcd. for $C_{11}H_{24}O_6$: C, 55.90; H, 10.23; MR, 61.5. Found: C, 55.70; H, 10.36; MR, 60.6.

Hydrolysis of the mixture yielded ethanol, 2-ethoxyethanol, and a little liquid boiling at 185–195°, taken to be 2-(2-ethoxyethoxy)ethanol. The kind and quantity of alcohols produced by hydrolysis indicate that III predominated but that some II was present also.

1-Diethoxymethoxy-2-[2-(2-ethoxyethoxy)ethoxy]ethane (*IV*), *1-[ethoxy-(2-ethoxyethoxy)methoxy]-2-(2-ethoxyethoxy)ethane* (*V*) *and tris-(2-ethoxyethoxy)methane* (*VI*) were obtained as a mixture boiling at 184–187° (35 mm.), n_D^{20} 1.4208, d_{20} 0.9887, yield 7 g. (15%).

Anal. Calcd. for $C_{13}H_{28}O_6$: C, 55.69; H, 10.06; MR, 72.5. Found: C, 55.84; H, 10.36; MR, 71.8.

Hydrolysis of the mixture yielded ethanol, 2-ethoxyethanol, a liquid boiling at 194–197° (n_D^{20} 1.4237), evidently 2-(2-ethoxyethoxy)ethanol, and some still higher-boiling material. Since only a very little liquid boiling above 197° was obtained, no direct identification was made. However, its mode of formation and its high boiling point indicate that it was 2-[2-(2-ethoxyethoxy)ethoxy]ethanol. The kind and quantity of alcohols formed by hydrolysis products indicate that VI predominated in the mixture.

Methyl orthoformate and ethylene oxide. Methyl orthoformate (318 g., 3 moles), ethylene oxide (50 ml., 1 mole) and boron trifluoride (1.5 g., 0.02 mole) were caused to react as before. After the ethyl ether, methyl orthoformate degradation products, and excess methyl orthoformate were removed, 30 g. (20%) of 1-dimethoxymethoxy-2-methoxyethane (VII) was obtained, b.p. 172–174° (743 mm.), n_D^{20} 1.4012, d_2 1.001.

Anal. Calcd. for $C_6H_{14}O_4$: C, 47.99; H, 9.39; MR, 36.4. Found: C, 48.09; H, 9.41; MR, 36.5.[5]

VII was characterized by hydrolysis in 6*N* hydrochloric acid to (a) methanol, yielding the α-naphthylurethan, m.p. 118.5–119.5°, and (b) 2-methoxyethanol, also characterized as the α-naphthylurethan, m.p. 112–113°.[4]

The residue from VII distilled with decomposition even at reduced pressure.

Ethyl orthoformate and propylene oxide. Ethyl orthoformate (450 g., 3 moles), propylene oxide (30 g., 0.5 mole) and boron trifluoride (1.5 g., 0.02 mole) were caused to react as before. After the preliminary fractions had been removed, further distillation at reduced pressure through a Todd column gave three principal portions.

Fraction 1, consisting of the isomeric 1:1 adducts of propylene oxide and ethyl orthoformate, boiled at 113–119° (36 mm.) n_D^{20} 1.4040, d_2 0.9123, yield 39 g. (37%). No attempt was made to separate or characterize the individual isomers.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75; MR, 55.0. Found: C, 57.99; H, 11.12; MR, 55.3.

Fraction 2, consisting of the isomeric 2 propylene oxide: 1 ethyl orthoformate adducts, had b.p. 151–153° (36 mm.) n_D^{20} 1.4169, d_{20} 0.9411, yield 26 g. (20%). Again no attempt was made to separate or characterize isomers.

Anal. Calcd. for $C_{13}H_{28}O_6$: C, 59.05; H, 10.67; MR, 70.7. Found: C, 58.40; H, 10.71; MR, 70.6.

Fraction 3, consisting of the isomeric 3 propylene oxide: 1 ethyl orthoformate adducts, boiled at 172–174° (36 mm.), n_D^{20} 1.4211, d_{20} 0.9572, yield 18 g. (11%).

(1) Abstracted from a thesis submitted by Frank Bier Slezak in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Oklahoma Agricultural and Mechanical College, 1955.

(2) Present address: Diamond Alkali Company, Painesville, Ohio.

(3) O. C. Dermer and A. M. Durr, *J. Am. Chem. Soc.*, 76, 912 (1954).

(4) N. D. Cheronis and J. B. Entrikin, *Semimicro Qualitative Organic Analysis*, Thomas Y. Crowell Company, New York, N. Y., 1947.

(5) Analyses by Geller Laboratories, New York, N. Y.

Anal. Calcd. for $C_{16}H_{34}O_6$: C, 59.59; H, 10.62; MR, 86.4. Found: C, 59.71; H, 10.94; MR, 85.4.

Acknowledgment. This work was sponsored by the Cities Service Research and Development Company in the form of a research fellowship.

DEPARTMENT OF CHEMISTRY
OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE
STILLWATER, OKLA.

The Addition of Hydrogen Bromide to Allyl Chloride[1]

JAMES G. TRAYNHAM AND JOHN S. CONTE

Received December 7, 1956

The ionic addition of hydrogen bromide to allyl chloride would appear to be a rather simple reaction, which should follow Markownikoff's rule. However, conflicting reports have appeared in the literature. Shostakovskii[2] reported an unusual dependence of orientation on temperature; the addition reaction yielded 1-chloro-2-bromopropane exclusively at 18°, 1-chloro-3-bromopropane at −19°, and equal amounts of the two isomers at 0°. That same year Antsus,[3] referring to Shostakovskii's work, claimed that the orientation is independent of temperature (−19° to 18°) and that in all cases he obtained only 1-chloro-2-bromopropane. Although the earlier paper has been quoted in a recent review,[4] Antsus' work appears to have been overlooked.

Because an actual temperature dependence such as was claimed[2] would be theoretically significant, we have reexamined the ionic addition of hydrogen bromide to allyl chloride with particular attention to olefin purification,[5] exclusion of air and light,[5] and possibilities of product isomerization. The procedures previously described[2,3] were followed closely. Products were identified by comparison of physical and spectral properties with those of authentic samples independently synthesized.

Contrary to both previous reports,[2,3] mixtures of isomers were obtained in all experiments. Except in those experiments in which we failed to exclude air completely, the product distribution was virtually invariable with Markownikoff orientation predominating (90 ± 2%). The orientation was independent of temperature (−18° to 18°), of the use of acetic acid solvent, and of reaction time. When air was admitted, the peroxide-effect[5] led to greatly altered product distributions. No isomerization could be detected when either of the two isomeric products (1-chloro-2-bromopropane and 1-chloro-3-bromopropane) was treated with hydrogen bromide under the same conditions used in the addition reactions. This observation precludes the possibility that either chlorobromopropane is an intermediate in the formation of the other. That is, they are formed independently in the reaction mixture, probably from two different intermediates or transition states.

Based on the report[6] that some migration of chlorine occurs in the addition of hypochlorous acid to Cl^{36}-labeled allyl chloride, an attempt was made to detect 1-bromo-2-chloropropane in the product mixture. Infrared spectral analysis[7] did indeed suggest the presence of very small amounts of this isomer mixed with the 1-chloro-2-bromopropane fraction, but conclusive evidence was not obtained.

EXPERIMENTAL[8]

Independent synthesis of the chlorobromopropanes. 1-Chloro-2-bromopropane and 1-chloro-3-bromopropane were prepared from phosphorus tribromide (0.27 mole) and the appropriate chloropropanol (0.53 mole). After the initial addition of phosphorus tribromide at 0°, the mixture was allowed to warm to room temperature and was stirred for 10 hr. longer. The 1-chloro-2-bromopropane[9] was obtained in 77% yield; b.p. 118–120°, n_D^{20} 1.4776, d_4^{20} 1.537. The 1-chloro-3-bromopropane[9] was obtained in 75% yield; b.p. 140–142°, n_D^{20} 1.4866, d_4^{20} 1.592. The infrared spectra of the two isomers were similar but were readily distinguished by the following non-common bands (s and m refer to strong- and medium-intensity absorption, respectively; numbers refer to wavelength in microns): for 1-chloro-2-bromopropane, 7.25 (s), 8.90 (m), 9.00 (m), 9.95 (s), 11.05 (s); for 1-chloro-3-bromopropane, 7.56 (s), 10.50 (s), 11.65 (s), 11.90 (s).

A small amount of 1-bromo-2-chloropropane[9b] was prepared in poor yield from thionyl chloride and 1-bromo-2-propanol (b.p. 67–70°/40 mm., n_D^{20} 1.4760, d_4^{20} 1.542; obtained in 62% yield by the reaction of 48% hydrobromic acid with propylene oxide[10]). In the one preparation attempted, the amount of 1-bromo-2-chloropropane obtained

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(7) When one product mixture was distilled, several fractions boiling in a 1° range were collected. The infrared spectra of those boiling between 115° and 117° (very small amounts of material) showed medium-intensity absorption at 9.05 μ. This band gradually disappeared in the spectra of the fractions boiling between 118° and 122°. The independently prepared 1-bromo-2-chloropropane, alone of the three isomers, showed absorption at 9.05 μ.

(8) All infrared spectra were obtained with a Perkin-Elmer Model 21 double-beam recording infrared spectrophotometer (0.05 mm. cells, NaCl windows)

(9) (a) I. Heilbron, "Dictionary of Organic Compounds," p. 479, Oxford University Press, London, 1953 (b) A. Dewael, *Bull. soc. chim. Belges.*, **39**, 87 (1930).

(10) E. Abderhalden and E. Eichwald, *Ber.*, **51**, 1320 (1918).

was not sufficient for adequate determination of physical properties. The infrared spectrum indicated slight contamination by alcohol; in other regions the spectrum was quite similar to that of 1-chloro-2-bromopropane except for a medium-intensity band at 9.05 μ not found in the latter. Since the product mixture from the addition reactions contained only very small amounts, if any, if 1-bromo-2-chloropropane, no further attempts to prepare this isomer were made.

Addition reactions. With acetic acid solvent. Solutions prepared in nitrogen-filled flasks from glacial acetic acid (50 g.), anhydrous hydrogen bromide (45 g., 0.56 mole), and allyl chloride (0.26 to 0.65 mole) were kept in cold rooms at 18°, 0°, or −18° (±1°) for 2 to 6 weeks. The shorter reaction times were generally used with the more concentrated solutions and usually led to recovery of more allyl chloride. Each solution was poured into 150 g. of ice water. The lower layer was separated, washed with dilute sodium carbonate and with water, dried, and distilled. After most of the allyl chloride had been removed, the infrared spectrum of the residual liquid was recorded. The product composition was estimated by comparing this spectrum with those obtained with pure samples and known mixtures of allyl chloride and the isomeric chloro bromides. In nearly all experiments, this estimation was confirmed by distillation of the residual liquid.

In 7 experiments (2 each at 18° and 0°, 3 at −18°), yields (based on unrecovered allyl chloride) of chlorobromopropanes were in the range 64–81%. The product mixtures were composed of 1-chloro-2-bromopropane (90 ± 2%) and 1-chloro-3-bromopropane (10 ± 2%). In 2 other experiments, the reaction flasks became unstoppered during the long period of standing and the product distributions were greatly altered (49% and 78% 1-chloro-3-bromopropane).

Without solvent. Anhydrous hydrogen bromide (122 g., 1.5 moles) was added during 5 hr. to allyl chloride (50 g., 0.65 mole) in an atmosphere of nitrogen. The solution was kept in a cold room for 2 to 3 weeks and was subsequently processed in the manner described for the experiments with solvent. In 4 experiments (2 each at −18° and 18°) the product mixtures, obtained in 65–71% yields, were composed of 1-chloro-2-bromopropane (91 ± 1%) and 1-chloro-3-bromopropane (9 ± 1%). In one experiment (at 0°) from which air was not excluded completely, the lower yield of product mixture was mainly 1-chloro-3-bromopropane (92%).

Attempted isomerizations of addition products. Solutions prepared by adding 10.0 g. (0.064 mole) of 1-chloro-2-bromopropane or of 1-chloro-3-bromopropane to a mixture of 10.0 g. (0.12 mole) of anhydrous hydrogen bromide and 10.0 g. of glacial acetic acid were kept at 18° for 6 days. The chloro bromides were recovered by dilution of the solutions with water. Washing, drying, and distillation led to recovery of 98–99% of the starting chlorobromopropane. No isomerization could be detected.

COATES CHEMICAL LABORATORIES
LOUISIANA STATE UNIVERSITY
BATON ROUGE, LA.

Formylation of Thianaphthene with *N*-Methylformanilide

V. V. GHAISAS[1]

Received December 13, 1956

The formation of thiophenecarboxaldehyde by direct formylation of the thiophene nucleus employing *N*-methylformanilide and phosphorus oxychloride was reported.[2] By modification of the procedure, Weston and Michaels[3] were able to obtain a 9% yield of a compound thought to be 3-thianaphthenecarboxaldehyde, when thianaphthene was allowed to react with *N*-methylformanilide in the presence of phosphorus oxychloride. Although the product melted at 58°, the same melting point as the 3-isomer, these investigators reported that it formed a phenylhydrazone melting at 204–205°. On the other hand, Komppa and Weckman[4] reported the melting point of this derivative to be 115°.

The work has now been reinvestigated. Thianaphthene was formylated,[3] and a compound melting at 58° was obtained in 7% yield. However, the phenylhydrazone of this product melted at 115°, which agrees with the one reported in the literature.[4] The melting points of the oxime and the semicarbazone[5] also agreed with those of the 3-isomer to be found in the literature.

The 3-isomer was then obtained from 3-chloromethylthianaphthene by applying the Sommelet reaction.[2] The melting point of this product was not depressed by admixture with the one prepared by formylation of thianaphthene. The ultraviolet absorption spectrum of the compound obtained by formylation showed that it has a molecular extinction coefficient of 8526 at its maximum at 302 mμ. This, however, does not assist in differentiating between the two isomers.

EXPERIMENTAL

The absorption spectrum was taken on a Beckman quartz spectrophotometer using a 1.14×10^{-4} molar solution of the aldehyde in 95% ethanol.

RESULTS

The results give evidence that formylation of thianaphthene with *N*-methylformanilide gives 3-thianaphthenecarboxaldehyde.

Acknowledgments. This study was supported by grants of the National Science Foundation and the U. S. Public Health Service. The thianaphthene used was obtained through the courtesy of Dr. W. J. Coppoc of the Texas Company, Beacon, N. Y.

COMMUNICATION NO. 328 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

(1) Post-doctoral Fellow from the University of Bombay, India.

(2) King and Nord, *J. Org. Chem.*, **13**, 635 (1948).

(3) Weston and Michaels, *J. Am. Chem. Soc.*, **72**, 1422 (1950).

(4) Komppa and Weckman, *J. prakt. Chem.*, **138**, 109 (1933).

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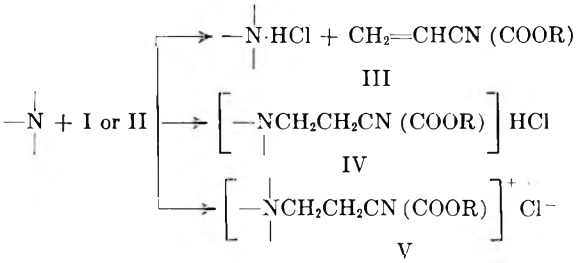
Reactions of 3-Chloropropionitrile and Alkyl 3-Chloropropionates with Amines

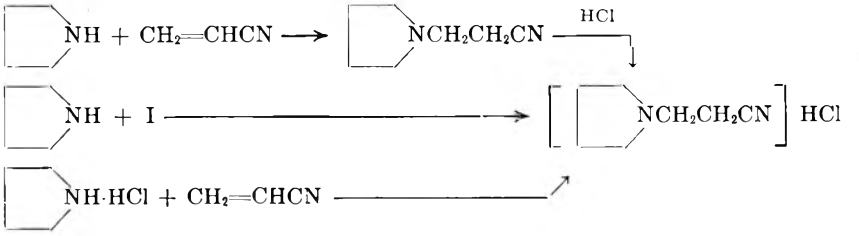
S. Allen Heininger

Received December 13, 1956

Numerous reports exist in the literature concerning the reaction of 3-chloropropionitrile (I) and alkyl 3-chloropropionates (II) with basic materials. With triethylamine,[1] quinoline,[2] diethylaniline,[3] or alcoholic sodium hydroxide,[4] I and II undergo dehydrochlorination leading to amine hydrochlorides and the corresponding acrylic compound. It has now been shown that reaction of I or II with amino compounds can give amine hydrochlorides (III), 3-aminopropionitrile hydrochlorides (IV), or quaternary salts (V), depending upon the nature of the amine.



Primary or secondary aliphatic amines, upon reaction with I in refluxing ethanol, gave high yields of the corresponding 3-aminopropionitrile hydrochlorides (IV) as shown in Table I. With tertiary aliphatic amines, dehydrochlorination of I and production of the tertiary amine hydrochloride (III) results.[5] The formation of IV from primary and secondary amines may occur by either of two routes: dehydrochlorination and subsequent cyanoethylation of the amine hydrochloride, or a one-step concerted displacement-rearrangement reaction. While the actual mechanism by which IV is formed has not been established, the feasibility of the former route was demonstrated by cyanoethylating pyrrolidine hydrochloride in refluxing ethanol to give good yields of 3-(1-pyrrolidinyl)-propionitrile hydrochloride. This product was identical with the hydrochloride prepared from 3-(1-pyrrolidinyl)propionitrile and with the product obtained by the reaction of I with pyrrolidine. Cyanoethylation of amine hydrochlorides has not previously been reported.



With aromatic amines the behavior of I and II is again dependent upon the nature of the amine. With aniline, I gave only III upon refluxing in ethanol. While cyanoethylation of aromatic amines is known to be acid-catalyzed[6] (and aniline hydrochloride has been reported to catalyze cyanoethylation of aniline[7]), cyanoethylation of aniline hydrochloride apparently did not occur under the reaction conditions employed.

Heterocyclic aromatic amines react with I or II to give III or V by dehydrochlorination or quaternization reactions, respectively, as shown in Table I. Pyridine, with either I or II, readily gave quaternary salts ranging from crystalline to gelatinous solids. With II, yields decreased with increasing size of the alkyl group. With methyl or benzo-substituted pyridines, the location of the substituent group dictates whether quaternization or dehydrochlorination predominates. In the picoline series, reaction of α-picoline and I gave only α-picoline hydrochloride, while both β- and γ-picoline quaternized with I in high yields. Reaction of I with the isomeric quinolines showed a similar difference; whereas quinoline caused only dehydrochlorination of I, isoquinoline gave an 86% yield of 1-(2-cyanoethyl)isoquinolinium chloride. Thus, α-substituted or α,β-benzo-substituted pyridines are sufficiently hindered sterically that dehydrochlorination of I is the predominant reaction, while under the same conditions the β- or γ-substituted or β,γ-benzo-substituted pyridines quaternize readily with I, as does pyridine itself.

In contrast, 2-ethylhexyl 3-chloropropionate reacted with quinoline to give the carbalkoxyethyl quinolinium chloride in 5% yield with no dehydro-

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(2) C. S. Marvel, *J. Am. Chem. Soc.*, 62, 3495 (1940).
(3) C. Moureu, M. Murat, and L. Tampier, *Ann. chim. (Paris)* [9] 15, 21 (1921).
(4) W. Bauer, to Rohm and Haas, U. S. Patent 1,864,884 (1932).
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(6) H. A. Bruson, *Org. Reactions*, V, 85–86 (1949).
(7) A. F. Bekhli and A. G. Serebrennikov, *J. Gen. Chem. U.S.S.R.*, 19, 1553 (1949); *Chem. Abstr.*, 44, 3448 (1950).
(8) H. Wagner, *Z. Kryst. Mineral.*, 43, 167, 176 (1907).
(9) F. Ullmann, *Ber.*, 31, 1699 (1898).

TABLE I

REACTION OF $ClCH_2CH_2Q$ WITH AMINES

Amine	Q	Time hr.	% Product III	% Product IV	% Product V	m.p.[a] °C.	Formula	Calcd. C	Calcd. H	Calcd. Cl	Calcd. N	Found C	Found H	Found Cl	Found N
Ammonia[b]	CN	0.5	97	8.4	—	126–128	$C_3H_7ClN_2$	—	—	—	26.3	—	—	—	26.4
n-Butylamine	CN	72	—	82	—	176–177	$C_7H_{15}ClN_2$	51.6	9.3	21.8	17.2	51.2	9.1	21.5	17.1
Pyrrolidine	CN	72	—	89	—	171–173	$C_7H_{13}ClN_2$	52.4	8.2	—	17.4	52.8	7.4	—	17.0
Morpholine	CN	24	—	84	—	212.5–213	$C_7H_{13}ClN_2O$	47.9	6.9	20.1	15.9	46.9	7.6	19.2	15.2
Trimethylamine	CN	1.0	95	—	—	>255[c]	—	—	—	—	—	—	—	—	—
Triethylamine	CN	1.0	96	—	—	255–256[d]	—	—	—	—	—	—	—	—	—
Aniline	CN	24	55	—	—	193–194[e]	—	—	—	—	—	—	—	—	—
Pyridine	CN	92	—	—	91	145–148	$C_8H_9ClN_2$	—	—	21.0	16.6	—	—	20.9	17.4
"	$COOC_2H_5$	90	—	—	87	waxy	$C_{10}H_{14}ClNO_2$	—	—	16.5	6.5	—	—	17.7	7.3
"	$COOC_4H_9$	72	—	—	83	waxy	$C_{11}H_{18}ClNO_2$	—	—	14.6	5.8	—	—	14.9	6.4
"	$COOC_8H_{17}$	72	—	—	88	jelly	$C_{16}H_{26}ClNO_2$	—	—	11.8	4.7	—	—	12.6	4.7
"	$COOC_9H_{19}$	72	—	—	70	jelly	$C_{17}H_{28}ClNO_2$	—	—	11.7	4.6	—	—	12.4	4.5
"	$COOC_{13}H_{27}$	90	—	—	42	jelly	$C_{21}H_{36}ClNO_2$	—	—	9.6	3.8	—	—	10.9	3.8
Quinoline[f]	CN	87	85	—	—	114–117	—	—	—	—	—	—	—	—	—
"	$COOC_8H_{17}$	69	—	—	5.7[g]	waxy	—	—	—	—	—	—	—	—	—
Isoquinoline	CN	87	—	—	86	220–222	$C_{12}H_{11}ClN_2$	65.9	5.1	16.2	12.8	65.3	5.3	16.1	11.7
Quinaldine	CN	48	79	—	—	220–221	$C_{10}H_{10}ClN$	67.5	5.6	19.8	7.8	67.1	5.8	19.4	7.5
8-Quinolinol	CN	69	77	—	—	228–229	C_9H_8ClNO	59.6	4.5	19.6	7.7	59.9	4.5	19.6	7.7
α-Picoline	CN	48	98	—	—	75–77	C_6H_8ClN	55.6	6.2	27.4	10.8	54.5	6.5	25.5	10.7
β-Picoline	CN	72	—	—	88	65–75[h]	$C_9H_{11}ClN_2$	—	—	19.4	15.4	—	—	20.5	13.6
γ-Picoline	CN	72	—	—	90	161–163	$C_9H_{11}ClN_2$	59.3	6.1	19.4	15.4	58.6	6.3	19.2	15.0
Acridine	CN	72	85	—	—	233–235	$C_{13}H_{10}ClN$	72.5	4.7	16.5	6.5	72.5	5.1	16.1	6.7

[a] Uncorrected. [b] Excess aqueous NH_3 used; isolated also 80% $NH(CH_2CH_2CN)_2$ from liberated acrylonitrile. [c] Reported m.p. 277–278°.[8] [d] Reported m.p. 253–254°.[8] [e] Reported m.p. 198°.[9] [f] With benzene as solvent, 51 hr. gave 72% III. [g] Infrared examination showed COOR and aliphatic CH absorption. [h] Crude product could not be recrystallized from ethanol-ether.

chlorination observed. That the quaternary salt from II could be isolated while that from I was not, is possibly attributable to the relative electronegativities of the cyano and ester groups in I and II; β-elimination occurring more readily with the group possessing the greater electron-withdrawing effect.

EXPERIMENTAL

The following general procedure was used in the reaction of 3-chloropropionitrile and alkyl 3-chloropropionates with amines. To a solution of the amine in absolute ethanol (200–300 ml. per mole) was added an equimolar quantity of the 3-chloropropionic acid derivative. With aliphatic amines the reaction was usually exothermic, while no temperature rise was noted with most aromatic amines. The resulting solution was refluxed from 0.5 to 90 hr., and the ethanol was distilled off under reduced pressure until solidification occurred. The residue was washed with anhydrous ether to remove unreacted starting materials and ethanol, and dried in a vacuum oven at 40–50°. The products obtained with a variety of amines are reported in Table I. Those from I were generally crystalline solids (either IV or V), while those from II ranged from waxy solids to gels. Recrystallization, where possible, was from ethanol-ether mixtures. All products (III, IV and V) were hygroscopic.

1-(2-Cyanoethyl)pyrrolidinium chloride. This material was prepared by reaction of pyrrolidine and I, from hydrogen chloride and 3-(1-pyrrolidinyl)propionitrile, and by cyanoethylation of pyrrolidine hydrochloride. A solution of 43 g. (0.4 mole) of pyrrolidine hydrochloride, 21 g. (0.4 mole) of acrylonitrile, and 80 ml. of absolute ethanol was refluxed for 72 hr., and worked up as above to give 55 g. (90%) of a slightly yellowish solid. One recrystallization from ethanol-ether gave white plates, m.p. 168–170°, of 3-(1-pyrrolidinyl)-propionitrile hydrochloride. A mixed melting point of this material and that prepared by reaction of I and pyrrolidine (Table I) was not depressed.

CENTRAL RESEARCH DEPARTMENT
MONSANTO CHEMICAL CO.
DAYTON 7, OHIO

Arylthiomethyl Quaternary Ammonium Salts from the Alkylation of Some Dialkylaminomethyl Aryl Sulfides

GERALD F. GRILLOT AND HAROLD G. THOMPSON

Received December 17, 1956

Grillot *et al.*[1] have prepared in this laboratory dialkylaminomethyl aryl sulfides by the condensation of secondary amines and formaldehyde with thiophenols. It was of interest to us to determine if alkylation of these aminomethyl sulfides with an equivalent of an alkyl halide would produce quaternary ammonium salts rather than sulfonium salts. This was to be expected on the basis of reports by Kirchner, Soria, and Cavallito[2] who prepared quaternary ammonium salts of dialkylaminopropyl alkyl sulfides by allowing the latter to react with methyl and ethyl iodide and of Renshaw and Searle[3] who earlier observed that ammonium salt formation took precedence over sulfonium salt formation when the nitrogen and sulfur in an aminoalkyl alkyl sulfide were separated by from one to three carbon atoms.

Since alkylation of dimethylaminomethyl phenyl sulfide by benzyl chloride produces a salt which is identical to the benzyl phenylthiomethyl dimethylammonium chloride prepared by Barber and Green[4] by the action of *N,N*-dimethylbenzylamine on phenyl chloromethyl sulfide,[5,6] then in these aminomethyl aryl sulfides alkylation must occur preferentially on the nitrogen atom. In this latter synthesis it was found to be more satisfactory to prepare phenyl chloromethyl sulfide by the method of Bordwell and Pitt[7] than by Barber's method.[5,6]

Data concerning a group of new phenylthiomethyl trialkylammonium iodides and picrates prepared by the action of an alkyl iodide on a dialkylaminomethyl phenyl or *p*-chlorophenyl sulfide are listed in Table I.

It was expected that the quaternary ammonium iodides formed would be crystalline since crystallinity is a general characteristic of this type of salt. However there are several instances in the literature where compounds of this nature are not crystalline. For instance, Barber and Green[4] found that some of the quaternary salts prepared from *N,N*-dimethylbenzylamine were oils. Renshaw and Searle[3] found that derivatives obtained from methyl iodides were highly crystalline, while those from ethyl iodide tended to form oils. A characteristic common to these oils is the bulkiness of at least one of the substituents attached to the nitrogen. It appears possible that these large groups prevent the molecules from orienting themselves into a crystal structure.

EXPERIMENTAL

Benzyl phenylthiomethyl dimethylammonium chloride. Method A. Thioanisole was prepared by the method of Gilman and Beaber.[8] The fraction distilling at 69–71°/11 mm., obtained in a yield of 91%, was collected. The boiling point reported in the literature[8] is 58–60°/6 mm.

The method of Bordwell and Pitt[7], in which thioanisole is treated with sulfuryl chloride, was employed in the preparation of phenyl chloromethyl sulfide. The latter compound was obtained as an oil boiling at 85–87°/3 mm. in a yield of

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(2) F. K. Kirchner, A. E. Soria, and C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 4599 (1955).

(3) R. R. Renshaw and D. E. Searle, *J. Am. Chem. Soc.*, **59**, 2056 (1937).

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(7) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

(8) H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, **47**, 1449 (1925).

TABLE I

TRIALKYL ARYLTHIOMETHYLAMMONIUM IODIDES AND PICRATES

Cation	Iodide: Melting Point, °C.	Iodide: Analysis % Carbon Calcd.	Iodide: Analysis % Carbon Found	Iodide: Analysis % Hydrogen Calcd.	Iodide: Analysis % Hydrogen Found	Picrate: Melting Point °C.	Picrate: Analysis % Carbon Calcd.	Picrate: Analysis % Carbon Found	Picrate: Analysis % Hydrogen Calcd.	Picrate: Analysis % Hydrogen Found
Phenylthiomethyl triethylammonium	150.4–152.2[a,b]					121–122.4	50.43	50.71	5.35	5.52
Ethyl phenylthiomethyl piperidinium	oil					90.6–92	51.72	52.05	5.21	5.40
Ethyl phenylthiomethyl morpholinium	oil					102.6–104	48.92	48.79	4.75	4.88
Ethyl *p*-chlorophenylthiomethyl morpholinium	oil					133–135	45.56	45.42	4.23	4.34
Ethyl *p*-chlorophenylthiomethyl piperidinium	oil[c]					131.4–133	48.14	48.33	4.65	4.80
Phenylthiomethyl triethylammonium	152.4–154[a,d]	38.84	39.09	5.216	5.363	126–127.6	46.82	46.96	4.42	4.74
p-chlorophenylthiomethyl triethylammonium	155–156[d,e]	40.47	40.35	5.488	5.338	103.8–105	46.86	47.40	4.76	4.94

Picrates recrystallized from ethyl alcohol. Carbon and hydrogen analysis performed by Drs. Weiler and Strauss, 164 Banbury Road, Oxford, England.

[a] Recrystallized from ethyl acetate. [b] Yield about 25%. [c] Yield about 28% based on yield of crude sample. [d] Recrystallized from ethyl acetate-chloroform mixture. [e] Yield about 20%.

47%. Bordwell and Pitt[4] reported a boiling point of 103–104°/12 mm.

Benzyl phenylthiomethyl dimethylammonium chloride was obtained by the action of *N*,*N*-dimethylbenzylamine on phenyl chloromethyl sulfide according to the procedure of Barber *et al.*[4] The crude product was obtained in a yield of 84% and melted at 164–170°. After recrystallization from a chloroform-ethyl acetate mixture, it melted at 168–171°. The melting point previously reported was 161–165°.[4] The picrate melted at 125–126°, (literature; 124–125°).

Method B. Dimethylaminomethyl phenyl sulfide was prepared by adding dropwise 20.5 ml. (0.2 mole) of thiophenol to 13 ml. (0.2 mole) of cold dimethylamine and then adding to the resulting mixture 18 g. (0.2 mole) of formalin. This reaction mixture was heated at 80° for 2 hr. and after cooling was extracted with ether. The ether extract was dried over anhydrous $MgSO_4$. After removal of the ether, a fraction boiling at 112–116°/9–11 mm. was obtained in a yield of 23.8 g. or 71%.

Benzyl phenylthiomethyl dimethylammonium chloride was then prepared by following the general method described by Wagner and Zook.[9,10]

To a solution of 8.4 g. (0.05 mole) of dimethylaminomethyl phenyl sulfide in 20 ml. of benzene was added 5.8 ml. (6.33 g.; 0.05 mole) of benzyl chloride. After standing for 17 hr. 3 g. of material separated. If the mother liquor was heated for 4 hr. at 60° an additional 2.7 g. of the product precipitated giving combined a yield of 40%. After two recrystallizations from a chloroform-ethyl acetate mixture it melted at 170.2–171° and gave no depression of the melting point when mixed with the quaternary ammonium salt prepared by Barber's method.

This chloride salt was converted to the picrate which melted at 124.8–125.4° and gave no depression of the melting point when mixed with the picrate obtained by the method of Barber.

Trialkyl phenylthiomethylammonium iodides. General method. The dialkylaminomethyl aryl sulfide, prepared by the method previously described by Grillot *et al.*,[1] was dissolved in a small volume of benzene and to this solution was added an equivalent quantity of ethyl or methyl iodide. If a crystalline precipitate did not form at once, the reaction mixture was heated at 60° until either a crystalline product or an oily residue formed. Although many of these compounds were oils that would not crystallize, all could be converted to crystalline picrates. Melting points, solvents for recrystallization, and analytical data for the crystalline iodides and picrates obtained are detailed in Table I.

CHEMISTRY DEPARTMENT
SYRACUSE UNIVERSITY
SYRACUSE, 10, N. Y.

(9) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, Method 436, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 668.

(10) R. S. Shelton, M. G. Van Campen, C. H. Tilford, H. C. Lang, L. Nisonger, F. J. Bandelin, and H. L. Rubenkoenig, *J. Am. Chem. Soc.*, 68, 753, 755, 757 (1946).

Synthesis of Potential Anticancer Agents. V. Convenient Synthesis of 4(5)-Amino-5(4)-carboxamido-1,2,3-triazole[1]

L. L. BENNETT, JR. AND HARRY T. BAKER

Received December 17, 1956

The ribotide of 4-amino-5-imidazolecarboxamide (AIC) has been implicated for some time as an intermediate in biosynthesis of purines.[2] Since many of the agents that temporarily inhibit growth of

(1) This work was supported by a grant from the American Cancer Society. For the preceding paper in this series, see ref. 4.

(2) See, among others, (a) G. R. Greenberg, *Federation Proc.*, 13, 745 (1954). (b) M. P. Schulman and J. M. Buchanan, *J. Biol. Chem.*, 196, 513 (1954).

neoplasms are known to inhibit purine synthesis,[3] analogs of AIC are of interest as potential anticancer agents. As part of a study of compounds which might interfere with the imidazole intermediates in biosynthesis of purines,[4] the 1,2,3-triazole analog of AIC and some related compounds were prepared. While this paper was in preparation, Hoover and Day[5] reported the preparation of 4(5)-amino-5(4)-carboxamido-1,2,3-triazole and a number of other triazoles. However, our method of preparation of this analog of AIC was different from theirs and is of some interest in that this method apparently has not been employed hitherto in the triazole series.

The success of Taylor and co-workers[6,7] in preparing a number of 3-amino-5,6-diphenylpyrazinamides by the aminolytic cleavage of 6,7-diphenyllumazine suggested that this method might be applied conveniently to the preparation of 4(5)-amino-5(4)-carboxamido-1,2,3-triazole from 8-azaxanthine. It was found that this triazole could be obtained in good yield when 8-azaxanthine[8,9] was heated with ammonium hydroxide essentially under the conditions used by Taylor[6] for the conversion of 6,7-diphenyllumazine to 3-amino-5,6-diphenylpyrazinamide. Acetylation of the triazole gave a diacetyl derivative which showed the lability toward water characteristic of some other ring-acylated nitrogen heterocycles[10] and readily lost one acetyl group to give 4(5)-acetamido-5(4)-carboxamido-1,2,3-triazole.

By other methods, two phenyl derivatives of this triazole were also prepared as potential antagonists of AIC. When phenylazide and cyanoacetamide were allowed to react under conditions commonly used for synthesis of triazoles from azides and active methylene compounds,[5,11,12] 1-phenyl-4-carboxamido-5-amino-1,2,3-triazole was obtained in high yield. This compound, when heated with pyridine, underwent rearrangement to a product that, by analogy with rearrangements reported for a number of triazoles of similar structure,[12] was formulated as 4(5)-carboxamido-5(4)-phenylamino-1,2,3-triazole. The esters corresponding to both of these triazole carboxamides are known compounds,[12] but attempts to prepare the amides from the esters were unsuccessful.

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(4) L. L. Bennett and H. T. Baker, *J. Am. Chem. Soc.*, **79**, 2188 (1957).

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(6) E. C. Taylor, *J. Am. Chem. Soc.*, **74**, 1651 (1952).

(7) E. C. Taylor, J. A. Carbon, and D. R. Hoff, *J. Am. Chem. Soc.*, **75**, 1904 (1953).

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(9) L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948).

(10) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956).

(11) O. Dimroth, *Ber.*, **35**, 4041 (1902).

(12) O. Dimroth, *Ann.*, **364**, 183 (1909).

EXPERIMENTAL[13]

4(5)-Amino-5(4)-carboxamido-1,2,3-triazole. 8-Azaxanthine[9] (5.0 g.) and 200 ml. of concentrated ammonium hydroxide were placed in a small steel bomb. While the bomb was rocked, the temperature was raised to 195–200° (about 1 hr. required) and then kept at 175–185° for 4 hr. At the end of this time the bomb was cooled rapidly to room temperature and opened, after which the clear amber liquid, which rapidly darkened on standing, was transferred to a flask. The triazole was precipitated as the silver salt which was washed thoroughly with water, then suspended in water, and finally decomposed with hydrogen sulfide. The filtrate resulting from removal of silver sulfide was concentrated to dryness *in vacuo* leaving an almost colorless residue. Crystallization from water gave 2.3 g. of colorless crystals, m.p. 223.5–224.0°; reported,[5] 224–225°. Concentration of the mother liquor gave a second crop of 0.59 g., a total yield of 70%. A sample for analysis was recrystallized several times from water and dried at 56° *in vacuo*.

Anal. Calcd. for $C_3H_5N_5O$: C, 28.35; H, 3.97; N, 55.10. Found: C, 28.33; H, 4.15; N, 55.22.

Spectral Data. λ_{max} in mμ (a_M): pH 7–226 (9.71×10^3), 261 (9.74×10^3); pH 10–266 (9.84×10^3). $\bar{\nu}$ in cm.$^{-1}$: 1625 (primary amino group); 1660 (amide carbonyl). The ultraviolet spectrum at pH 7 agrees well with that reported[5] in 50% ethanol.

For preparation of the diacetyl derivative 0.10 g. of the compound was dissolved in a boiling solution of 3 ml. of acetic anhydride and 0.5 ml. of acetic acid. After being boiled for 5 min., the solution was cooled and the white precipitate which resulted was washed with alcohol and ether; wt. 0.12 g., m.p. 210–212°.

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.17. Found: C, 39.62; H, 3.98; N, 33.10.

The infrared spectrum showed strong absorption at 1735 cm.$^{-1}$ and a shoulder at 1715 cm.$^{-1}$; heterocycles containing a ring *N*-acyl group are known to absorb in this region.[14] This compound was therefore formulated as 4(5)-acetamido-5(4)-carboxamido-1,2,3-triazole with a second acetyl group on one of the ring nitrogen atoms.

When the diacetyl derivative (0.055 g.) was boiled for 5 min. in 3 ml. of water, crystals began to separate from the hot solution. After the solution had been cooled, the solid was separated and washed with cold water. The colorless product weighed 0.035 g. (79%), melted at 267–268°, and analyzed as a monoacetyl derivative. The infrared spectrum showed that absorption in the range 1700–1750 cm.$^{-1}$, characteristic of the ring acyl group, had been destroyed by the treatment with water.

Anal. Calcd. for $C_5H_7N_5O_2$: C, 35.50; H, 4.17. Found: C, 35.55; H, 4.40.

1-Phenyl-4-carboxamido-5-amino-1,2,3-triazole. This compound was prepared essentially by the method used by Dimroth[12] for the synthesis of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole, except that cyanoacetamide was used in place of ethyl cyanoacetate.

To a solution of cyanoacetamide (5.65 g.) in 150 ml. of absolute ethanol there were added in succession a sodium ethylate solution (prepared from 42 ml. of absolute ethanol and 1.5 g. of sodium) and 8.0 g. of phenyl azide. There was an immediate precipitation of solid and the mixture became sufficiently hot to require cooling. After a few minutes, the solid redissolved. After the amber solution had been allowed to stand for three days, the voluminous solid was collected and washed with ethanol; wt. 12.0 g. (87%). For preparation of an analytical sample, a portion was recrystallized once from water and three times from ethanol. The product melted at 162–163°; the melt solidified at 165–167° and the

(13) Melting points are uncorrected. Infrared spectra were run in pressed potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer.

(14) W. Otting, *Chem. Ber.*, **89**, 1940 (1956).

solid then melted again at about 200°. The melting points varied with the duration of heating. This behavior is probably due to thermal rearrangement which has been reported[12] to occur in related triazoles.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.19; H, 4.46; N, 34.47. Found: C, 52.94; H, 4.32; N, 34.32.

Spectral Data. λ_{max} in mμ (a_M) in absolute alcohol: 225 (10.2×10^3), 253 (shoulder) (9.50×10^3). The spectrum was similar to that of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole, prepared according to Dimroth.[12]

4(5)-Carboxamido-5(4)-phenylamino-1,2,3-triazole. For rearrangement of 1-phenyl-4-carboxamido-5-amino-1,2,3-triazole, the conditions used were those reported by Dimroth[12] for the rearrangement of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole to 4(5)-carbethoxy-5(4)-phenylamino-1,2,3-triazole. After the 1-phenyl derivative had been refluxed in pyridine for 3 hr., the reaction mixture was cooled and neutralized with hydrochloric or acetic acid to precipitate the triazole. The triazole, thus obtained in 75% yield, melted at 200–201° after being recrystallized from absolute ethanol. The elemental analysis was the same as that of the starting material. The ultraviolet absorption spectrum, determined in absolute ethanol, had maxima at 262 mμ (a_M, 10.2×10^3) and at 297 mμ (a_M, 9.93×10^3) and was similar to that found for 4(5)-carbethoxy-5(4)-phenylamino-1,2,3-triazole.[12]

Acknowledgments. The authors wish to thank Drs. Glynn P. Wheeler and John A. Montgomery for helpful suggestions; Mr. J. P. Holmquist for elemental analyses; and Dr. W. C. Coburn and Mr. J. W. Murphy for infrared spectra determinations.

KETTERING-MEYER LABORATORY[15]
SOUTHERN RESEARCH INSTITUTE
BIRMINGHAM, ALA.

(15) Affiliated with Sloan-Kettering Institute.

New Trifluoromethylphenothiazine Derivatives

PAUL N. CRAIG, EDWARD A. NODIFF, JOHN J. LAFFERTY, AND GLENN E. ULLYOT

Received January 22, 1957

We wish to make a preliminary report of some physical and chemical data on aminoalkyl fluorine-substituted phenothiazines with pronounced pharmacological activity.[1,4] Phenothiazine drugs containing halogen or methoxyl substituents have been discussed by Viaud.[2] Smith has reported several trifluoromethylphenothiazines,[3] but no 10-aminoalkyl derivatives thereof have been described chemically. A preliminary report on the pharmacological activity of compounds 2 and 9 (Table III) has been presented.[4a,b] A brief clinical report[4c] on the antiemetic and psychotherapeutic effectiveness of com-

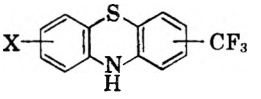
(1) The pharmacology of these drugs will be published in detail elsewhere by Dr. Leonard Cook and coworkers of these laboratories.

(2) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954).

(3) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(4) (a) J. C. Burke, H. L. Yale, G. L. Hassert, Jr., and J. P. High, Program, The American Society for Pharmacology and Experimental Therapeutics Meeting, French Lick, Ind., Nov. 8–10, 1956, p. 11. (b) J. J. Piala, J. P. High, K. Greenspan, and J. C. Burke, Program, The American Society for Pharmacology and Experimental Therapeutics Meeting, French Lick, Ind., Nov. 8–10, 1956, p. 11. (c) P. K. Conner, W. Fraser, S. I. Kinard, H. Bennett, and J. H. Moyer, *Clin. Res. Proc.*, 5 (1), 121 (1957).

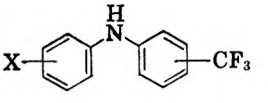
TABLE I



X	CF_3 (Position)	M.P., °C.[a]	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H[b]	4	71–72°	5	$C_{13}H_8F_3NS$	58.42	3.02	5.24	58.54	3.18	5.38
8-Cl	2	188–189°	8.5	$C_{13}H_7ClF_3NS$	51.75	2.34		52.10	2.59	
7-OCH_3	2	169–170°	19	$C_{14}H_{10}F_3NOS$	56.56	3.39	4.71	56.63	3.62	4.75

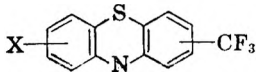
[a] Uncorrected. [b] Prepared by H. E. Reiff and J. Jaffe of these (SKF) Laboratories.

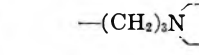
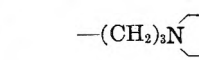
TABLE II



X	CF_3 (Position)	B.P., °C.	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3-Cl	3′	128–9°/0.05 mm.	57	$C_{13}H_9ClF_3N$	57.47	3.34	5.16	57.41	3.37	5.26
4-OCH_3	3′	m.p. 59–60°	41	$C_{14}H_{12}F_3NO$	62.92	4.53	5.24	63.00	4.65	5.16

TABLE III



No.	CF_3 (Position)	R	X	B.P., °C.	M.P., °C.[a]	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
1	2[b]	$-CH_2CH_2N(CH_3)_2$	H	152.5°/0.3 mm.	239.5–240° (HCl)	$C_{17}H_{18}ClF_3N_2S$	54.47	5.84	54.66	4.97
2	2	$-CH_2CH_2CH_2N(CH_3)_2H$?	H	177–181°/1 mm.	176–177° (HCl)	$C_{18}H_{20}ClF_3N_2S$	55.59	5.21	55.70	5.22
3	2	$-(CH_2)_3N(CH_3)_2$	H		214–5° (HCl)	$C_{18}H_{20}ClF_3N_2OS$	53.39	4.98	53.11	5.08
4	2[c]		H	202–210°/0.7 mm.	193–194° (dimaleate)	$C_{29}H_{32}F_3N_3O_8S$	54.45	5.04	54.53	5.17
5	2[d]		H	---	173–175° di HCl	$C_{21}H_{26}Cl_2F_3N_3OS$ .3 H_2O	45.82	5.86	45.50	5.92
6	2	$-(CH_2)_3N(CH_3)_2$	7-OCH_3	205–210°/0.8 mm.	177.5–179° (HCl)	$C_{19}H_{22}ClF_3N_2OS$	54.47	5.29	54.77	5.53
7	2	$-(CH_2)_3N(CH_3)_2$	8-Cl	195–202°/1.3 mm.	114–116° (maleate)	$C_{22}H_{22}ClF_3N_2SO_4$	52.54	4.41	52.61	4.70
8	2	$-(CH_2)_3N(CH_3)_2$	8C-H_3	188–191°/0.5 mm.	153–154° (maleate)	$C_{23}H_{25}F_3N_2O_4S$	57.25	5.22	57.42	5.20
9	4	$-(CH_2)_3N(CH_3)_2$	H	185–190°/0.3 mm.	147–148° (HCl)	$C_{18}H_{20}ClF_3N_2S$	55.59	5.18	55.59	5.11

[a] Uncorrected (oil bath). [b] Prepared by A. M. Pavloff, SKF Laboratories. [c] Prepared by B. M. Lester, SKF Laboratories. [d] Prepared by E. L. Anderson, SKF Laboratories.

pounds 2 and 4 (Table III) has also been published recently.

The compounds in Table III were prepared by alkylation of the appropriate phenothiazine with a tertiary aminoalkyl halide in an inert solvent, using sodamide as a condensing agent.[5] In Table I are listed the parent trifluoromethylphenothiazines prepared in this work which have not been described elsewhere.

The substituted phenothiazines were prepared by the method of Bernthsen,[6] using the appropriately substituted diphenylamines. The diphenylamines which have not been described elsewhere are listed in Table II. An alternative route to the trifluoromethylphenothiazines is found in the Smiles rearrangement.[7]

The sulfoxides listed in Table III were prepared by the action of hydrogen peroxide on the oxalate salts of the parent compound.[8]

4-Trifluoromethylphenothiazine (m.p. 71–72°) was isolated in yields of less than 5% as a side-product in the thionation of 3-trifluoromethyldiphenylamine. Its configuration as the 4-isomer was indicated by the peak in infrared at 12.5 microns, found in 1,2,3-trisubstituted benzene[9] rings, and by the absence of a peak at 12–12.1 microns, found in 2-trifluoromethylphenothiazine[3] and other 1,2,4-trisubstituted benzene compounds.[9]

Acknowledgment. The authors wish to express their appreciation to Mr. E. S. Rump, Mrs. Doris A. Rolston, Miss Joan R. McCafferty, and Miss Margaret A. Carroll of these laboratories for the infrared data and elemental analyses reported above.

RESEARCH AND DEVELOPMENT DIVISION
SMITH, KLINE AND FRENCH LABORATORIES
PHILADELPHIA, PA.
RESEARCH INSTITUTE OF TEMPLE UNIVERSITY
PHILADELPHIA, PA.

(5) Compare P. Charpentier, U. S. Patent 2,645,640 (July 14, 1953).
(6) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).
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Preparation of 2,2′-Diaminobiphenyl by Reduction of 2,2′-Dinitrobiphenyl

A. E. BLOOD AND C. R. NOLLER

Received January 29, 1957

Attempts to prepare 2,2′-diaminobiphenyl from 2,2′-dinitrobiphenyl by chemical reduction according to methods reported in the literature and by various modifications of these methods gave erratic results. Occasionally good yields of the diamine were obtained, but frequently the products were unreacted dinitrobiphenyl, tar, benzo[*c*]cinnoline-5-oxide, or benzo[*c*]cinnoline-5,6-dioxide or various mixtures.

Catalytic reductions in general were more satisfactory. The procedure of S. D. Ross, Kahan, and Leach[1] using ethanol-ethyl acetate (1 v.: 3 v.) and Adams catalyst gave uniformly good yields. The amount of catalyst and time of reduction can be reduced if the hydrogenation is carried out at an elevated temperature. Thus a solution of 12 g. of 2,2′-dinitrobiphenyl in 200 cc. of mixed solvent with 0.006 g. of platinum oxide, which was placed in the hydrogenator at 60°, was reduced in 20 min., whereas a run of the same size using 0.1 g. of catalyst which was started at room temperature required 30 min. The addition of six drops of 6*N* acetic acid had no effect on the rate at room temperature. The addition of six drops of 6*N* aqueous sodium hydroxide greatly reduced the rate of hydrogenation for about 25 min., but then the rate approached that of the neutral or acidic runs. Evidently alkali decreases the rate but is removed by reaction with the ethyl acetate. Reductions in ethanol[2] have the disadvantage that only about 1 g. of dinitrobiphenyl can be dissolved in 200 cc. and that the rate of reduction is somewhat slower than in the mixed solvent. Neither acid nor base has an appreciable effect on the rate in this solvent.

Everett and W. C. J. Ross[3] report that catalytic reduction of an ethanol solution of 2,2′-dinitrobiphenyl in ethanol in the presence of Raney nickel gave benzo[*c*]cinnoline. The present work shows, however, that under the proper conditions W-2 Raney nickel[4] gives excellent yields of 2,2′-diaminobiphenyl. An initial gauge pressure of around 50 p.s.i. is preferred. At pressures of 600 p.s.i. and at 2000 p.s.i. the results were erratic, tars and benzo-[*c*]cinnoline-5-oxide being among the products obtained. The ethanol-ethyl acetate (1 v.:3 v.) mixture was preferable as a solvent to methanol, ethanol, or dioxane. The usual concentration in this solvent was 12 g. per 200 cc. The rate of reduction definitely was dependent on the age of the catalyst. In a series of standard runs using 4 cc. of catalyst mush, starting with the solution at 60° and using catalyst that was 0, 6, 12, 20, and 24 months old, the time for complete reduction of 12 g. was 20,

(1) S. D. Ross, G. J. Kahan, and W. A. Leach, *J. Am. Chem. Soc.*, **74**, 4122 (1952).
(2) R. B. Carlin and W. O. Forshey, Jr., *J. Am. Chem. Soc.*, **72**, 800 (1950).
(3) J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1981 (1949).
(4) R. Mozingo, *Org. Syntheses*, Coll. Vol. 3, 181 (1955)

20, 110, 370, and 540 min. The addition of either acid or alkali to an old catalyst increased the rate of reduction. Thus a catalyst that brought about reduction in 510 min. in neutral solution, required 141 min. when two drops of 6*N* acetic acid was added, and 71 min. when two drops of 6*N* sodium hydroxide was added. The same effects were noted when ethanol was used as a solvent.

Solutions after reduction in the mixed solvent, using either Adams catalyst or Raney nickel, always were pale yellow and recrystallization from ethanol gave brown plates melting at 76–78°. Attempts to decolorize the solutions with Norit only intensified the color. To obtain pure material the product was distilled at 150–151° at 3 mm. The distillate was crystallized from a concentrated solution in ethanol to give colorless plates, m.p. 79–80°. Melting points of 80–81° and of 81° have been recorded.[1,5]

Recently the hydrogenation of benzo[*c*]cinnoline to 2,2′-diaminobiphenyl using Raney nickel catalyst was reported.[6] During the course of the present work benzo[*c*]cinnoline-5,6-dioxide was hydrogenated to benzo[*c*]cinnoline using either Raney nickel or Adams catalyst, but further reduction to 2,2′-diaminobiphenyl did not take place.

Department of Chemistry
Stanford University
Stanford, Calif.

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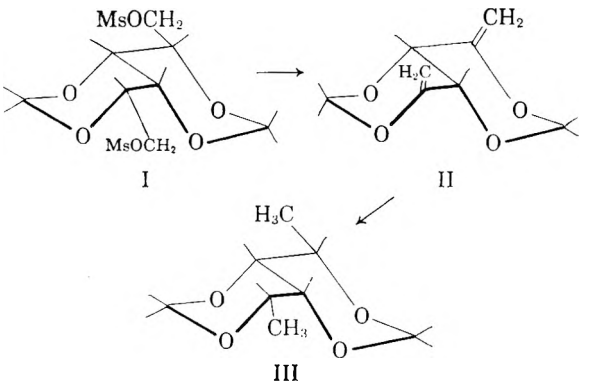
Conversion of 1,6-Di-*O*-methylsulfonyl-2,4:3,5-di-*O*-methylene-L-iditol to D-*threo*-4,8-Dimethylene-1,3,5,7-naphthodioxane

Erik Vis[1] and Hewitt G. Fletcher, Jr.

Received January 31, 1957

While formation of double bonds through loss of the elements of an alkyl or aryl sulfonic acid from adjacent carbon atoms under alkaline conditions has been reported repeatedly as an unwanted side reaction in the carbohydrate field,[2] the phenomenon has not received the study it deserves. We wish to report the very facile formation of the diene II from the dimesyl ester of the well-known 2,4:3,5-di-*O*-methylene-L-iditol (I).[3]

The structure of the diene was demonstrated through hydrogenation to 1,6-dideoxy-2,4:3,5-di-*O*-methylene-L-iditol (III), a substance which Hann and Hudson[3] have prepared through reduction of 1,6-dideoxy-1,6-diiodo-2,4:3,5-di-*O*-methylene-L-iditol. It is noteworthy that the diequatorial product III rather than the corresponding D-mannitol or D-glucitol analogs were isolated after the reduction of II. A crystalline tetrabromide prepared from



II is also reported here. Conformational and mechanistic considerations indicate that both the bromomethyl groups in this substance are probably equatorial although evidence on this point is lacking.

EXPERIMENTAL[4]

1,6-Di-O-methylsulfonyl-2,4:3,5-di-O-methylene-L-iditol (I). 2,4:3,5-Di-*O*-methylene-L-iditol (16.5 g.), prepared by the method of Hann and Hudson,[3] was "mesylated" in pyridine solution with methanesulfonyl chloride in normal fashion to yield a crystalline product which, recrystallized from acetone-pentane, 2-butanone, and methyl Cellosolve amounted to 20.0 g. (69%). The pure product melted at 163–164°, $[\alpha]_D^{20}$ +26° in chloroform (*c* 0.8).

Anal. Calcd. for $C_{10}H_{18}O_{10}S_2$: C, 33.14; H, 5.01; S, 17.70. Found. C, 33.37; H, 5.37; S, 17.70.

D-threo-4,8-Dimethylene-1,3,5,7-naphthodioxane (II). 1,6-Di-*O*-methylsulfonyl-2,4:3,5-di-*O*-methylene-L-iditol (6.28 g.) was added to 30 ml. of dry methyl Cellosolve in which 0.95 g. of sodium had been dissolved and the resulting mixture refluxed for 20 min. One volume of benzene and one of ether were added to the cooled reaction mixture and the sodium mesylate (4.16 g., quantitative) removed after further cooling to 0°. The filtrate, diluted with more benzene, was washed twice with water, dried over sodium sulfate, and concentrated *in vacuo* at room temperature. The crystalline residue, recrystallized twice from dichloromethane-pentane at Dry-Ice temperature and dried briefly *in vacuo* (30 mm.) at 20°, weighed 1.7 g. (58%), m.p. at 80°, $[\alpha]_D^{20}$ +269.5° in acetone (*c* 0.56). The product has a significant vapor pressure and prolonged drying results in considerable loss.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.36; H, 5.89.

The infrared absorption spectrum of the diene showed the absence of hydroxyl and carbonyl functions and had bands at 3.5 and 3.6 μ (C—H stretching) and 6.0 μ (C=C).

1,6-Dideoxy-2,4:3,5-di-O-methylene-L-iditol (III). D-*threo-4,8-Di-methylene-1,3,5,7-naphthodioxane* (230 mg.) was dissolved in 3 ml. of glacial acetic acid and hydrogenated at 25°, platinum from 30 mg. of PtO_2 being used as catalyst. When the calculated quantity of hydrogen had been absorbed (35 min.) warm ethyl acetate was added to dissolve the partially precipitated product. The catalyst was removed and the solution concentrated *in vacuo* to a dry, crystalline

(1) Chemical Foundation Fellow 1956–1957.

(2) R. S. Tipson, *Advances in Carbohydrate Chem.*, **10**, 108 (1955).

(3) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **67**, 602 (1945).

(4) Melting points are corrected.

mass. Recrystallized from carbon tetrachloride the product (130 mg., 55%) melted at 208–210° either alone or in admixture with an authentic sample of 1,6-dideoxy-2,4-3,5-di-*O*-methylene-L-iditol.[3]

9,10-D-threo-4,8-Dibromo-4,8-di(bromomethyl)-1,3,5,7-naphthodioxane hexane. A solution of 470 mg. of the diene, II, in 5 ml. of carbon tetrachloride was treated at 0° with 7 ml. of a 4% (v/v) solution of bromine in the same solvent. The slight excess of bromine, together with the solvent was immediately removed *in vacuo* and the crystalline residue dissolved in hot cyclohexane. The resulting solution was treated with a trace of solid sodium bicarbonate and of alumina, filtered and diluted with pentane. At 0° the substance crystallized as elongated plates melting (after darkening at *ca.* 120°) at 135–150° and showing in acetone (c 3.35) $[\alpha]_D^{20}$ +210.0° (987 mg., 73%). After three recrystallizations from cyclohexane-pentane the material melted as before; $[\alpha]_D^{20}$ +208.1° in acetone (*c* 2.94).

Anal. Calcd. for $C_8H_{10}O_4Br_4$: Br, 65.26. Found: Br, 65.07.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE, U. S. DEPT. OF HEALTH, EDUCATION, AND WELFARE
BETHESDA 14, MD.

Preparation of Mono-*N*-alkyl and -*N*-Acyl Piperazines by Non-Hydrolytic Cleavage of 1-Carbethoxypiperazines

WILLIAM O. FOYE,[1] LESTER CHAFETZ,[2] AND EDWARD G. FELDMANN[3]

Received January 21, 1957

Recent discoveries have made piperazine derivatives important as medicinal agents, and a large number of 1,4-unsymmetrically substituted piperazines has been prepared for various purposes. Among them, a promising agent for the treatment and prophylaxis of both hemorrhagic[4] and heat shock[5] is the relatively simple structure, 1-ethyl-4-ethylsulfonylpiperazine. Because of the tedious method of synthesis available for this compound, an improved procedure was sought. Specifically, the use of a nonhydrolytic cleavage of 1-carbethoxy-4-substituted piperazines which would permit the preparation of both 1-alkyl and 1-acyl piperazines was investigated.

The hydrolytic procedures which have been described for decarbethoxylation of piperazine monourethans require conditions too drastic for use in the presence of other hydrolyzable functions such as amides or esters. Use of the benzyl group as a blocking agent for piperazines is also undesirable in cases where other groups may be reduced or may poison the catalyst during catalytic debenzylation. A mild, nonhydrolytic, nonreductive decarbethoxylation was therefore attempted with dry hydrogen bromide in glacial acetic acid. This reagent has previously been used for the removal of carbobenzoxy groups in peptides[6,7] and was found suitable for the preparation of mono-*N*-alkyl piperazines. For example, 1-carbethoxy-4-ethylpiperazine was cleaved to 1-ethylpiperazine dihydrobromide in 3 hr. with an 89% yield. The monosubstituted piperazines prepared by this method are shown in Table I. 1-Isopropylpiperazine dihydrobromide was also obtained but could not be satisfactorily purified.

To investigate the suitability of the hydrogen bromide cleavage method for 1-acylpiperazines, 1-benzoyl-4-carbethoxypiperazine was first selected. When a basic aqueous solution of 1-carbethoxypiperazine was treated with an excess of benzoyl chloride at room temperature, however, a good yield of 1,4-dibenzoylpiperazine resulted. This result is in contrast to the relatively slow hydrolysis of the carbethoxy group observed in either acid or alkali. The 1-benzoyl-4-carbethoxypiperazine was obtained by treatment with benzoyl chloride in pyridine, and the cleavage with hydrogen bromide was carried out at a temperature of 60–70° for 30 min. The product was found to be piperazine dihydrobromide, however.

Similar results were obtained using 1-carbethoxy-4-acetylpiperazine and 1-carbethoxy-4-benzenesulfonylpiperazine; both the carbethoxy and acyl groups were cleaved in each instance. No indication of cleavage was apparent, from the liberation of ethyl bromide and carbon dioxide gases, until a temperature of 60–70° was reached, which prevented the use of lower temperatures for this reaction. Reduction of the reaction time to a period of 5 to 10 min. (using quantities of 0.005 mole of substituted piperazine) also resulted in the formation of piperazine dihydrobromide, either pure or admixed with starting material.

A fair yield of a monoacyl piperazine was secured, however, from the cleavage of 1-carbethoxy-4-ethylsulfonylpiperazine. After removal of the piperazine dihydrobromide and several recrystallizations, a 39% yield of 1-ethylsulfonylpiperazine hydrobromide was obtained. Further search for optimum conditions for this cleavage has not been made, since the use of 1-carbobenzyloxypiperazines appeared more suitable and is presently being investigated for the preparation of 1-acylpiperazines.

No cleavages were observed at room tempera-

(1) Present address: Massachusetts College of Pharmacy, Boston, Mass., to which any requests should be directed.

(2) Wisconsin Alumni Research Foundation Fellow, 1953–1955.

(3) Fellow of the American Foundation for Pharmaceutical Education, 1953–1955.

(4) D. Bovet, S. Courvoisier, R. Ducrot, and R. Jacob, *Compt. rend.*, **227**, 1423 (1948).

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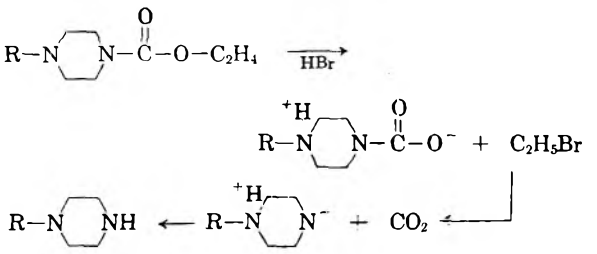
TABLE I

N-ALKYL AND *N*-ACYL PIPERAZINES FROM HBr CLEAVAGE R—N⟨⟩NH · 2HBr

R	M.P., °C.	Recrystallization solvent	Yield, %	Formula	Analyses, % Calcd.	Found[a]
CH_3	202–204	Absolute ethanol	85	$C_5H_{14}N_2Br_2$	N: 10.69	N: 10.44
C_2H_5	200–202	Absolute ethanol	89	$C_6H_{16}N_2Br_2$	C: 26.10	C: 26.36
					H: 5.84	H: 6.08
n-C_3H_7	224–230	Absolute ethanol	98	$C_7H_{18}N_2Br_2$	C: 28.98	C: 29.40
					H: 6.26	H: 6.15
$C_2H_5SO_2$[b]	216–217	Ethanol-ether	39	$C_6H_{15}N_2O_2SBr$	C: 27.81	C: 27.43
					H: 5.83	H: 5.95

[a] Analyses were obtained from the Clark Microanalytical Laboratory, Urbana, Ill., and the Weiler and Strauss Microanalytical Laboratory, Oxford, England. [b] The mono-hydrobromide was isolated.

ture, which is consistent with the observations of Ben-Ishai and Berger[6] that hydrogen bromide-acetic acid cleaves benzyl carbamates at room temperature to the amine hydrobromide, benzyl bromide, and carbon dioxide, while hydrogen chloride in acetic acid acts analogously at 75°. In the case of the ethyl carbamates, less tendency for nucleophilic attack by bromide would be expected to occur than with the benzyl carbamates, and bromide ion is a better nucleophile than chloride ion. This reaction may therefore be represented by equation I.



Equation I. Hydrogen bromide cleavage of carbethoxypiperazines.

EXPERIMENTAL[8]

Cleavage of 1-carbethoxy-4-alkylpiperazines by hydrogen bromide. In a 500-ml. flask fitted with a gas absorption trap was placed 37 g. (0.2 mole) of 1-carbethoxy-4-ethylpiperazine[9,10] and 250 ml. of a 1*N* solution of hydrogen bromide in glacial acetic acid, prepared by adding glacial acetic acid to 30–32% hydrogen bromide in glacial acetic acid (Eastman Organic Chemicals). The mixture was warmed on a steam bath, and after an induction period of 25 min., carbon dioxide and ethyl bromide were evolved. After the reaction had proceeded 3 hr. at 60°, it was cooled and filtered, yielding 12.5 g. of crystals. Additional product was obtained by pouring the filtrate into 950 g. of dry ether and chilling the resulting oil. A total yield of 49.0 g. (89%) of 1-ethylpiperazine dihydrobromide was obtained after recrystallization. The methyl, propyl, and isopropyl derivatives were obtained in the same manner.

1,4-Dibenzoylpiperazine. A chilled aqueous solution of 3.9 g. (0.02 mole) of 1-carbethoxypiperazine hydrochloride was treated with 5.6 g. (0.04 mole) of benzoyl chloride and 10% sodium hydroxide solution in the usual manner. A yield of 5.2 g. (88%) of 1,4-dibenzoylpiperazine resulted, m.p. 188–189° (lit.[11] m.p. 191°).

1-Benzoyl-4-carbethoxypiperazine. A solution of 4.8 g. (0.03 mole) of 1-carbethoxypiperazine hydrochloride in 100 ml. of dry pyridine was treated at 0° with 4.2 g. (0.03 mole) of benzoyl chloride. After being stirred for 2.5 hr., the mixture was poured into cold 5*N* sulfuric acid, and the resulting oil was extracted with ether. The extract was dried, evaporated, and crystallized from Skellysolve B, giving 5.5 g. of product melting at 96–98°. The yield was 70% of slightly impure compound.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.91. Found: C, 64.92; H, 6.56.

Cleavage of 1-benzoyl-4-carbethoxypiperazine by hydrogen bromide. A solution of 0.23 g. (0.001 mole) of 1-benzoyl-4-carbethoxypiperazine in 10 ml. of 15% hydrogen bromide in glacial acetic acid was heated at 70° for 30 min. and allowed to cool. The white, crystalline product was filtered, washed with ether and acetone, and dried. A yield of 0.07 g. of piperazine dihydrobromide was obtained which sublimed at 238°.

Anal. Calcd. for $C_4H_{12}N_2Br_2$: C, 19.37; H, 4.88. Found: C, 19.27; H, 5.14.

1-Carbethoxy-4-ethylsulfonylpiperazine hydrochloride. The ethylsulfonation procedure of Jacob[12] was used, and a 59% yield of product melting at 177–179° was obtained.

1-Ethylsulfonylpiperazine hydrobromide. A solution of 5.0 g. (0.02 mole) of 1-carbethoxy-4-ethylsulfonylpiperazine in 50 ml. of 1*N* hydrogen bromide in glacial acetic acid was warmed on a steam-bath for 0.5 hr. After cooling, the mixture was treated with 300 ml. of anhydrous ether, and the product was filtered. It was purified by digestion with 2 l. of hot absolute ethanol, filtration of the piperazine dihydrobromide, concentration to one-half volume, and addition of 2 l. of anhydrous ether. The product was twice recrystallized from ethanol-ether and once from absolute ethanol to give 2.0 g. of prisms melting at 216–217.5°. The yield was 39%.

SCHOOL OF PHARMACY
UNIVERSITY OF WISCONSIN
MADISON, WIS.

MASSACHUSETTS COLLEGE OF PHARMACY
BOSTON, MASS.

(8) All melting points were obtained on a Fisher-Johns block and are uncorrected.

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Reaction of Hexafluoropropene with Sulfur[1]

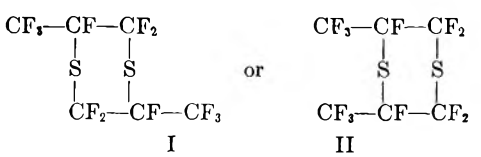
HENRY C. BROWN

Received May 21, 1956

Reports in the literature of fluorocarbon derivatives containing the typical monosulfide linkage are quite limited. Hauptschein and Grosse[2] in their preparation of the polysulfides $(C_3F_7)_2S_2$ and $(C_3F_7)_2S_3$ reported the formation of a trace of a compound that was thought to be $(C_3F_7)_2S$, but no identification was made. Haszeldine[3] prepared $(CF_3)_2S$ from the disulfide, $(CF_3)_2S_2$, by prolonged ultraviolet irradiation and found it to be quite stable to hydrolysis and unreactive in the usual organic sulfide reactions. In contrast, the fluorocarbon polysulfides are easily and completely hydrolyzed by dilute alkali.

Since the fluorocarbon monosulfides seem to approach the extreme stability of the fluorocarbon oxides and the fluorocarbon nitrides, interest has developed in synthesis of compounds containing this structural feature in order that their properties might be more fully studied.

Pyrolysis of n-C_3F_7COONa with an excess of sulfur at 300° produced a variety of products from which was separated a liquid fraction boiling at 112–113°. The molecular weight and analysis of this compound indicate an empirical formula $C_6F_{12}S_2$. The heterocyclic formula I or II is proposed



I or II

since this structure might result from the reaction of sulfur with $CF_3CF{=}CF_2$, known to be formed by pyrolysis of n-C_3F_7COONa.[4]

Reaction of hexafluoropropene, $CF_3CF{=}CF_2$, with an excess of sulfur produces, in higher yield, a compound with the same characteristics as the compound isolated from the pyrolysis of n-C_3F_7COONa in the presence of sulfur. This reaction supports the dithiane structure proposed above. The infrared absorption spectra of the compound prepared in this manner is shown in Figure 1. The disulfide structure is ruled out since this compound is stable to prolonged refluxing in aqueous alkali, whereas fluorocarbon polysulfides are easily hydrolyzed. This heterocyclic fluorocarbon is practically insoluble in water, alcohol, and carbon disulfide but soluble in a variety of solvents such as acetic acid, benzene, acetone, and carbon tetrachloride.

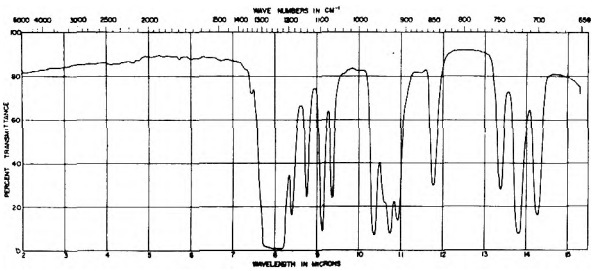


FIG. 1. INFRARED ABSORPTION SPECTRUM OF BIS(TRIFLUOROMETHYL)PERFLUORODITHIANE

EXPERIMENTAL

Pyrolysis of sodium heptafluorobutyrate in presence of sulfur. A mixture of 118 g. (0.5 mole) of sodium heptafluorobutyrate and 100 g. of sulfur was thoroughly mixed by grinding together in a dry atmosphere and the mixture was placed in a steel reaction vessel of 300-ml. capacity. The reactants were dried under vacuum at 120° for 1 hr.; the reactor was then sealed and heated to 300° for 12 hr. When the reactor had cooled to 160°, the total volatile reaction product was transferred through the vacuum system to a liquid air trap, and the trap was removed from the vacuum system and allowed to warm to room temperature. Volatile gases from the reaction product were retained in a Dry Ice–acetone cooled trap and identified as unreacted $CF_3CF{=}CF_2$ [5 g., mol. wt. 152 (Dumas)]. The remaining reaction product was refluxed with excess 10% sodium hydroxide solution for 18 hr., the water-insoluble layer separated and dried with anhydrous calcium chloride. Fractional distillation at atmospheric pressure gave 2 g., b.p. 112.0–113.0°; 16 g., b.p. 113.0–113.5° (mostly 113.0) n_D^{25}, 1.3390, 5 g. residue and column hold up.

Anal. Calcd. for $C_6F_{12}S_2$: C, 19.8; S, 17.6; mol. wt., 364. Found: C, 19.9; S 17.3; mol. wt., 366.

Reaction of hexafluoropropene with sulfur. Sulfur (130 g.) was placed in a steel reaction vessel of 300-ml. capacity, the vessel was evacuated and 117 g. (0.78 mole) $CF_3CF{=}CF_2$ was added through the vacuum system. The reactor was sealed and heated at 300° for 36 hr., then cooled to room temperature and the volatile product removed. Fractionation at atmospheric pressure gave the following cuts: (1) 19 g., b.p. 26.5–109.0 (not yet identified but distillation shows two flats at 46° and 55°); (2) 18 g., b.p. 109–112.8 (mostly 112.8); and (3) 68 g., b.p. 112.8–113.5. Fraction 3 (30 g.) was freed of traces of sulfur halides by refluxing with 10% sodium hydroxide for 18 hr., washed with water, and dried with calcium chloride. Fractionation gave (1) 2 g., b.p. 112.8–113.0; (2) 19 g., b.p. 113.0–113.3; (3) 2 g., b.p, 113.3–113.8, residue, 2 g.

Anal.[5] Fraction 2., C, 20.4; S, 17.1; mol. wt., 363; n_D^{25} 1.3406; d^{25}, 1.762. Calcd. for $C_6F_{12}S_2$, C, 19.8; S, 17.6; mol. wt., 364.

406 REED LABORATORIES
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.

(1) This work was supported in part by the Office of Naval Research under Contract N-Onr 580(03); NR 356-333 with the University of Florida. Reproduction in whole or in part is permitted for any purpose of the United States Government.

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(5) Molecular weights by Victor Meyer method. Carbon and sulfur analyses by Peninsular Chemical Research, Gainesville, Fla.

Kinetics and Mechanism of the Cyclization of Substituted Alkylnitroguanidines. II. 1-β-Bromoethyl-2-nitroguanidine; The Effect of Common Ion[1]

CARL BOYARS, HELEN CARY, AND VIVIAN STARK

Received January 11, 1957

In an earlier paper[1] the kinetics of the isomerization of some β- and γ-substituted 1-alkyl-2-nitroguanidines to 1-nitro-2-amino-1,3-diazacyclo-2-pentene and -hexene salts, respectively, have been reported. Based on the relative rates of reaction, an internal S_N2 mechanism was deduced. Confirmatory evidence for this mechanism can be obtained by studying the effect of excess anion on the reaction rate. This paper reports such data. Rate measurements have also been made on the cyclization of 1-β-bromoethyl-2-nitroguanidine.

EXPERIMENTAL

1-β-Chloroethyl- and 1-β-bromoethyl-2-nitroguanidine were synthesized according to the method of McKay and Milks.[2] The chloro compound was recrystallized as described in the previous paper. A microgravimetric determination[3] of chloride ion (carried out so as to minimize cyclization during the analysis[1]) showed none present. The bromo compound was not crystallized because it cyclizes too readily.[1] It was not readily soluble in water, and its aqueous solution did not give a positive test for bromide ion with silver nitrate solution. A portion of the bromo compound was converted to its cyclic isomer, 1-nitro-2-amino-1,3-diazacyclopentene-2-bromide, by dry heating at 65° for a few days. A portion of the chloro compound was converted to the analogous chloride salt by dry heating at 75° for 1 week. Microgravimetric determinations on the cyclic compounds showed 37.8% Br^- and 21.5% Cl^- (theoretical 37.9 and 21.3%, respectively).

The cyclization rate measurements in aqueous solution were carried out by the conductimetric technique with the apparatus previously used. The linear relationship expected between conductance and concentration of cyclic isomer (up to 200 mg./l.) in 0.00360*M* sodium chloride solution was found to hold. This concentration of sodium chloride is about the maximum that can be used without completely obscuring the effect of degree of cyclization on conductance. Rate measurements were made on 0.001235*M* 1-β-chloroethyl-2-nitroguanidine in this sodium chloride solution at 30.00° and on 0.000924*M* 1-β-bromoethyl-2-nitroguanidine in conductance water at 30.00 and 40.00°. Duplicate runs were made in each case. Rate constants were determined by the standard least squares procedure.

RESULTS AND DISCUSSION

Plots of the rate data based on conductance measurements show the expected first order linearity. The rate constant for the chloro compound in the presence of added chloride ion was computed using only data from the first 50 hr. (60% cyclized) of the run to eliminate effects of hydrolysis of the cyclic compound. The rate constant obtained, $4.69 \pm .04 \times 10^{-6}$ sec.$^{-1}$, when compared to that previously found in the absence of excess chloride ion (4.75×10^{-6} sec.$^{-1}$), shows that there is no common ion effect on the rate of cyclization. This is to be expected in the case of an S_N2 mechanism.

With the bromo compound, apparent deviations (due to hydrolysis) from the first order linearity of the reaction are noticeable only after the cyclization reaction is 80 to 85% complete. Because of the relatively rapid cyclization and the practice of allowing the solution to stand 0.5 hr. in the constant temperature bath before the initial reading, 35% of the linear compound at 30° and 55% at 40° had been cyclized before the first reading was taken. The kinetic data obtained were: $k_{30.00}$, $1.03 \pm .02 \times 10^{-4}$ sec.$^{-1}$; $k_{40.00}$, $3.645 \pm .005 \times 10^{-4}$ sec.$^{-1}$; energy of activation, E_a, $23.84 \pm .38$ kcal.; frequency factor, 1.59×10^{13} sec.$^{-1}$; entropy of activation, ΔS^*_{40}, -0.2 ± 1.2 e.u. Deviation measures are computed by the formulas of Purlee, Taft, and DeFazio.[4]

The rate of cyclization in aqueous solution of the bromo compound at 30° is 22 times that of the corresponding chloro compound.[1] Relative rates of this order of magnitude are in accordance with those expected from similar data on the rates of hydrolysis of *tert*-butyl, *tert*-amyl, and *sec*-octyl halides reported by Hughes and co-workers.[5-7] The lower energy of activation for the bromo as compared to the chloro compound[1] reflects the difference in bond energy between the C-Br and C-Cl links.

RESEARCH AND DEVELOPMENT DEPARTMENT
U. S. NAVAL POWDER FACTORY
INDIAN HEAD, MD.

(1) Paper I, C. Boyars, W. F. Sager, and S. Skolnik, *J. Am. Chem. Soc.*, **78**, 4590 (1956). Published with the permission of the Bureau of Ordnance, Navy Department. Opinions and conclusions are those of the authors.

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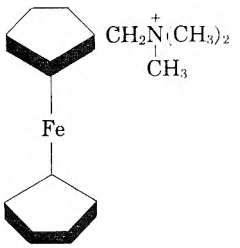
Communications TO THE EDITOR

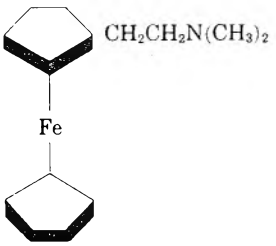
Some Reactions of the Methiodide of *N,N*-Dimethylaminomethylferrocene[1]

Sir:

Recently,[2] ferrocene was aminomethylated to form *N,N*-dimethylaminomethylferrocene, the methiodide of which (I) was rearranged by potassium amide in liquid ammonia to another tertiary amine. By analogy with the benzyltrimethylammonium ion, quaternary ion I was assumed to undergo the ortho substitution rearrangement. However, evidence has now been obtained that a rather unusual Stevens rearrangement occurs to form tertiary amine II, the methiodide of which was converted by potassium amide to vinylferrocene.[3] Amine II is being synthesized independently. The 1,2-shift of a methyl group does not occur as shown by synthesis of the product of such a reaction.

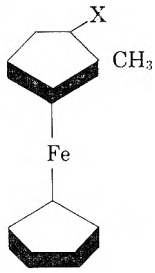


I



II

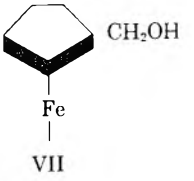
An unexpected ortho substitution type of reaction apparently occurs on treating quaternary ion I with aqueous sodium cyanide to form nitrile III (90%), m.p. 81–83° *Anal.*[4] Calcd. for $C_{12}H_{11}FeN$ C, 64.03; H, 4.93; N, 6.22; Fe, 24.81. Found: C, 64.00; H, 4.98; N, 6.05; Fe, 24.52. Reduction of this nitrile and dimethylation of the resulting primary amine produced in good yield a tertiary amine that was different from, but isomeric with, tertiary amine II obtained from the rearrangement. The tertiary amine prepared from the nitrile is presumably IV, b.p. 118–123° at 0.6 mm. *Anal.*[4] Calcd. for $C_{14}H_{19}FeN$: C, 65.38; H, 7.54; N, 5.45; Fe, 21.72. Found: C, 65.19; H, 7.32; N, 5.43; Fe, 21.37. *Methiodide*, m.p. 258° (dec.). *Anal.*[4] Calcd. for $C_{15}H_{22}FeIN$: C, 45.14; H, 5.56; N, 3.51; Fe, 13.99. Found: C, 45.34; H, 5.58; N, 3.51; Fe, 14.15. The methiodide of tertiary amine II melted at 248° (dec.); a mixed melting point with the methiodide of amine IV was 225–240°.



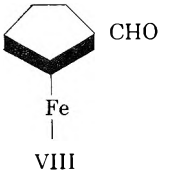
III (X = CN)
IV X = $CH_2N(CH_3)_2$
V (X = COOH)
VI (X = CH_2OH)

Nitrile III was hydrolyzed to acid V (94%), m.p. 154–156°. *Anal.*[4] Calcd. for $C_{12}H_2FeO_2$: C, 59.05; H, 4.96; 0, 13.11; Fe, 22.88. Found: C, 59.13; H, 5.07; Fe, 22.78. This acid was reduced to alcohol VI (86%) m.p. 41–41.5°. *Anal.*[4] Calcd. for $C_{12}H_{14}FeO$: C, 62.61; H, 6.13; Fe, 24.27. Found: C, 62.70; H, 6.04; Fe, 24.11. This alcohol was oxidized by "active" manganese dioxide[6] to the corresponding aldehyde (15%) which gave a strong carbonyl band in the infrared at 1680 cm.$^{-1}$ This band is also found in the spectrum of VIII. Such an oxidation is characteristic of benzyl type alcohols.[5] Attempts are being made to resolve such compounds as alcohol VI.

In contrast to sodium cyanide, sodium hydroxide has been shown[6] to react with quaternary ion I to form alcohol VII which on oxidation gives in good over-all yield aldehyde VIII. Several condensations of this aldehyde have been accomplished.[7] Recently,[8,9] aldehyde VIII was prepared by two other methods.



VII



VIII

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **21**, 382 (1956).

(3) We are indebted to Linde Air Products (Dr. R. L. Pruett) for an authentic sample of this compound.

(4) Analysis are by Galbraith Laboratories, Knoxville, Tenn.

(5) See R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 4399 (1955).

(6) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355(1957). A redetermination of the infrared spectrum of aldehyde VIII has given a maximum at 1681 cm.$^{-1}$ instead of 1690 cm.$^{-1}$

(7) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, in the hands of the editor.

(8) M. Rosenblum, *Chemistry and Industry*, 72 (1957).

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Work in progress includes the conversion of alcohol VII to the dibenzyl type ether, and of aldehyde VII to an amphoteric acid (by air oxidation). Rather surprisingly, both the iron and the aldehyde group in VIII were found to be somewhat resistant to oxidation with certain reagents. Thus, although the iron was readily oxidized by cerric sulfate, aldehyde VIII was recovered unchanged after treatment with 2% potassium permanganate in aqueous alcoholic solution (acidic or basic) for 10 min. on the steam bath. Apparently the type of oxidizing agent is important.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, N. C.

CHARLES R. HAUSER
JACQUE K. LINDSAY
DANIEL LEDNICER
CHARLES E. CAIN

Received April 22, 1957