TABLE II

Reactions of Primary Amines with Esters and Lithium Aluminum Hydride

Reagents				Molar Ratios[b]			Yield	
Ester	Amine	Amide Isolated[a]	Method	L/A	E/A	Hours at Reflux	of Amide, %	M.P.[c]
Ethyl benzoate	Aniline	Benzanilide	C	0.25	1.2	3	42	164–166[d]
Ethyl benzoate	Aniline	Benzanilide	C	0.25	1.2	3	37	164–166
Ethyl benzoate	Aniline	Benzanilide	A	1.5	3.0	18	17	164–165
Ethyl benzoate	Aniline	[e]	A	2.5	3.0	18	[e]	
Ethyl benzoate	Cyclohexylamine	Cyclohexylbenzamide	B	1.5	3.0	3	[f]	148–149[f]
Ethyl benzoate	Phenethylamine	[g]	A	3.0	3.0	18	[g]	
Ethyl acetate	Aniline	[h]	A	1.5	3.0	1	[h]	
Ethyl acetate	Cyclohexylamine	Cyclohexylacetamide	C	0.25	1.2	3	35	106–108[i]
Ethyl acetate	Cyclohexylamine	Cyclohexylacetamide	C	0.50	1.2	3	28	104–105
Ethyl acetate	Cydlohexylamine	Cyclohexylacetamide	A	1.5	3.0	18	37	108–109
Ethyl acetate	Cyclohexylamine	[g]	A	2.5	3.0	18	[g]	
Ethyl acetate	Phenethylamine	[g]	A	3.0	3.0	18	[g]	

[a] Alcohols and primary amines were also present in the reaction mixture. [b] L/A = lithium aluminum hydride/amine; E/A = ester/amine. [c] Uncorrected. Microanalyses were satisfactory. [d] A. F. Holleman *et. al.*, *Ber.*, **44**, 704 (1911) report m.p. 164°. [e] Infrared spectrum of product from ether extract of acid solution lacked a carbonyl band. Ether extract from alkaline solution did not contain amide or secondary amine. [f] Yield not determined. O. Wallach, *Ann.*, **343**, 40 (1905), reports m.p. 149°. [g] Ether extract from acid solution was not examined. Ether extract from alkaline solution did not contain amide or secondary amine. [h] Infrared spectrum of product contained a strong amide band. The reaction product was not purified. [i] A. Skita and H. Rolfes, *Ber.*, **53**, 1242 (1920), report m.p. 109°.

reaction of cyclohexylamine with 0.5 mole of lithium aluminum hydride was soluble in tetrahydrofuran; and yet we were unable to isolate alkylated products when such a solution was treated with esters. It appears, therefore, that some other factor, perhaps steric effects resulting from the polymeric structure of the primary amine/lithium aluminum hydride complexes, is more important in determining the course of this reaction.

EXPERIMENTAL

The picrates were prepared by adding an excess of ethanolic picric acid to a solution of the base in ethanol. The mixture was warmed on the steam bath for a few minutes and allowed to cool to room temperature. The picrate was filtered, washed with ethanol, dried in an oven at 65°, and submitted for analysis without further purification.

The amines were treated with the esters and lithium aluminum hydride by procedures essentially as described below.

Reactions of secondary amines with esters and lithium aluminum hydride (*Table I*). *Method A.* A solution of 0.1 mole of the amine in tetrahydrofuran was added dropwise to a solution of 0.2 mole of the lithium aluminum hydride in 250 ml. of tetrahydrofuran. Nitrogen gas was passed over the mixture during this addition. The reaction mixture was stirred for 15–30 min. and then heated to reflux temperature. A solution of the ester in about 2 parts of tetrahydrofuran was added dropwise over a period of about 1 hr. The reaction mixture was heated under reflux for 18 hr. and cooled. Eight milliliters of water, 24 ml. of 15% sodium hydroxide, and 24 ml. of water were added successively, and the solid was filtered off and washed with tetrahydrofuran. The mother liquor was treated with 20 ml. of concentrated hydrochloric acid and concentrated to remove the solvent. The residue was diluted with water and extracted with ether to remove nonbasic products. The aqueous layer was made alkaline and the basic products were extracted into ether and distilled.

Method B. The reaction was run as described above, except that hydrochloric acid was not added and the extractions were omitted.

Method C. A solution of 0.025–0.05 mole of lithium aluminum hydride in 50–100 ml. of tetrahydroduran was added dropwise to a solution of 0.1 mole of the amine in 50 ml. of tetrahydrofuran. A solution of 0.12 mole of the ester in 40 ml. of tetrahydrofuran was added and the mixture was heated under reflux for 3 hr. The reaction mixture was treated with water and 15% sodium hydroxide, filtered, and the mother liquor was concentrated to remove the solvent. The residue was triturated with ether or ethyl acetate, and filtered. If crystals did not form, the product was distilled.

Acknowledgment. We wish to thank Mr. L. Brancone and associates for the microanalyses.

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Reactive Methylene Compounds.
III. Attempted Syntheses of Cinnolines

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During the course of investigations on reactive methylene compounds,[2,3] the synthesis of cinnolines (II) by heating methyl 2,3-dioxobutyrate α-phenylhydrazones (I. R = substituted phenyl; R′ = CH_3) with sulfuric acid or anhydrous aluminum chloride was attempted. However, under the various conditions tried, only deesterification took place and the various acids thus obtained (I. R = substituted phenyl; R′ = H) are reported in Table I. The behavior is similar with ethyl

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[1] Present address: Central Drug Research Institute, Lucknow, India.

[2] H. G. Garg and S. S. Joshi, *J. Org. Chem.*, **26**, 946 (1961).

[3] H. G. Garg, *J. Org. Chem.*, **26**, 948 (1961).

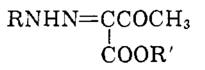
TABLE I

CHARACTERISTICS OF 2,3-DIOXOBUTYRIC ACID α-PHENYLHYDRAZONES

$$\underset{\displaystyle \overset{\|}{\text{NNHR}}}{\text{CH}_3\text{CO}\text{C}\text{COOH}}$$

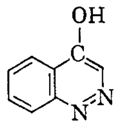
No.	R	M.P.	Method	Color	Formula	Found	Calcd.
1	Phenyl	149°	A	Pale yellow	$C_{10}H_{10}N_2O_3$	C, 58.08	58.25
						H, 4.62	4.85
						N, 13.26	13.59
2	4-Chlorophenyl	202°	A	Pale yellow	$C_{10}H_9ClN_2O_3$	Cl, 14.42	14.76
3	2-Chlorophenyl	128°	A	Pale yellow	$C_{10}H_9ClN_2O_3$	Cl, 14.51	14.76
4	4-Nitrophenyl	231°	B	Yellow	$C_{10}H_9N_3O_5$	N, 16.41	16.73
5	3-Nitrophenyl	192°	A & B	Yellow	$C_{10}H_9N_3O_5$	C, 47.99	47.80
						H, 3.68	3.58
						N, 16.55	16.73
6	2-Nitrophenyl	208°	A	Reddish brown	$C_{10}H_9N_3O_5$	N, 16.55	16.73
7	2,5-Dichlorophenyl	172°	B	Pale yellow	$C_{10}H_8Cl_2N_2O_3$	Cl, 25.62	25.81
8	2-Chloro-4-nitrophenyl	193°	A	Brown	$C_{10}H_8ClN_3O_5$	Cl, 12.21	12.43
9	2-Nitro-4-chlorophenyl	182°	A	Yellow	$C_{10}H_8ClN_3O_5$	Cl, 12.21	12.43

2,3-dioxobutyrate (I. R = substituted phenyl; R′ = C_2H_5). These acids were characterized by esterification with diazomethane to the known methyl esters.[4]



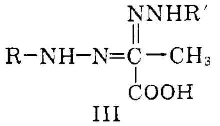
$$\text{RNHN}{=}\underset{\displaystyle\text{COOR}'}{\underset{|}{\text{C}}}\text{COCH}_3$$

I



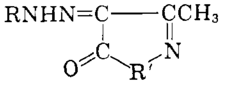
II

These hydrazones (I. R = substituted phenyl, R′ = H) on treatment with phenylhydrazine cyclized readily to the corresponding pyrazolones (IV. R = substituted phenyl; R = >N—C_6H_5); 2- or 4-nitrophenylhydrazone (III. R = 2- or 4-nitrophenyl; R′ = phenyl) could not be isolated and cyclized spontaneously to the corresponding pyrazolones (IV. R = 2- or 4-nitrophenyl; R′ =>N—C_6H_5). The 2,4-dinitrophenylhydrazones (III. R = substituted phenyl; R′ = 2,4-dinitrophenyl) of these hydrazones (I. R = substituted phenyl; R′ = H) could, however, not be cyclized even when refluxed with acetic acid or acetic anhydride for several hours.



$$\text{R–NH–N}{=}\underset{\displaystyle\text{COOH}}{\underset{|}{\overset{\displaystyle\text{NNHR}'}{\overset{\|}{\text{C}}}}}{-}\text{CH}_3$$

III



IV

The 2,3-dioxobutyric acids (I. R = substituted phenyl; R′ = H) on treatment with hydroxylamine yielded the corresponding isoxazolones (IV. R = substituted phenyl; R′ = —O—). The structure of these isoxazolones was confirmed by an unambiguous synthesis by the condensation of the appropriate benzenediazonium salts with 3-methyl-5-isoxazolone.[5] Mixed melting points in each case were undepressed.

Attempts to synthesize the cinnoline nucleus are still in progress.

EXPERIMENTAL[6]

Methyl 2,3-dioxobutyrate α-phenylhydrazones (I. R = substituted phenyl; R′ = CH_3) were prepared by coupling diazotized anilines with acetoacetic esters.[4]

Attempted cyclization of methyl 2,3-dioxobutyrates α-phenylhydrazones (I. R = substituted phenyl; R′ = CH_3). Method A. Methyl 2,3-dioxobutyrate α-3-nitrophenylhydrazone (1.0 g.) in concentrated sulfuric acid (15 ml.) was kept for several days at room temperature and poured over crushed ice. The product which separated was filtered and crystallized from acetic acid. Characteristics of the acids thus obtained are described in Table I.

Method B. Methyl 2,3-dioxobutyrate α-3-nitrophenylhydrazone (1.0 g.) dissolved in nitrobenzene (20 ml.)was heated with anhydrous aluminum chloride (2.0 g.) on a water bath for about 4 hr. The mixture was cooled, treated with ice and hydrochloric acid mixture, and washed repeatedly with water. Nitrobenzene was then removed by steam distillation and the product obtained crystallized as described above.

β-Phenylhydrazone of 2,3-dioxobutyric acid α-3-nitrophenylhydrazone (III. R = 3-nitrophenyl; R′ = C_6H_5). A solution of 2,3-dioxobutyric acid α-3-nitrophenylhydrazone (1.0 g.) in ethyl alcohol was mixed with an alcoholic solution of phenylhydrazine (0.43 g.) containing a few drops of acetic acid. Soon a precipitate of the bis(phenylhydrazone) separated as a yellow solid which was filtered and washed well with cold ethyl alcohol, m.p. 236°.

Anal. Calcd. for $C_{16}H_{15}O_4N_5$: N, 20.52. Found: N, 20.32.

1-Phenyl-3-methyl-4-(3-nitrobenzeneazo)-5-pyrazolone (IV. R = 3-nitrophenyl; R′ = >N—C_6N_5). A solution of III (R = 3-nitrophenyl; R′ = C_6N_5) (1.0 g.) in acetic acid (10 ml.) was refluxed for 1 hr. On cooling, the corresponding pyrazolone separated. Characteristics of the various pyrazolones thus prepared are given in Table II.

3-Methyl-4-(3-nitrobenzeneazo)-5-isoxazolone (IV. R = 3-nitrophenyl; R′ = —O—). Method A. A mixture of I (R = 3-nitrophenyl; R′ = H) (1.0 g.) in ethyl alcohol, hydroxylamine hydrochloride (0.28 g.), and excess sodium acetate was refluxed for 3 hr., cooled, and diluted with water. The isoxazolone thus obtained was crystallized from acetic acid.

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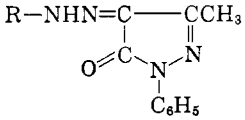
(4) H. G. Garg and S. S. Joshi, *J. Indian Chem. Soc.*, **37**, 626 (1960).

(5) L. Knorr and B. Reuter, *Ber.*, **25**, 1169 (1894).

(6) Melting points are uncorrected.

TABLE II

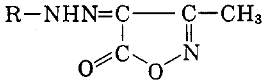
CHARACTERISTICS OF 1-PHENYL-3-METHYL-4-(SUBSTITUTED BENZENEAZO)-5-PYRAZOLONES



No.	R	Yield, %	M.P.	Color	Formula	Found	Calcd.
1	Phenyl	72	156°	Orange red	$C_{16}H_{14}N_4O$	N, 19.88	20.14
2	4-Chlorophenyl	78	142°	Orange red	$C_{16}H_{13}ClN_4O$	Cl, 10.98	11.36
3	2-Chlorophenyl	74	182°	Orange red	$C_{16}H_{13}ClN_4O$	Cl, 11.08	11.36
4	3-Nitrophenyl	79	180°	Orange red	$C_{16}H_{13}N_5O_3$	N, 21.42	21.67
5	2-Nitrophenyl	79	212°	Brownish red	$C_{16}H_{13}N_5O_3$	N, 21.36	21.67
6	2,5-Dichlorophenyl	79	224°	Orange red	$C_{16}H_{12}Cl_2N_4O$	Cl, 20.18	20.46
7	2-Chloro-4-nitrophenyl	80	223°	Deep red	$C_{16}H_{12}ClN_5O_3$	Cl, 9.62	9.93
8	2-Nitro-4-chlorophenyl	80	284°	Dull red	$C_{16}H_{12}ClN_5O_3$	Cl, 9.93	9.93

TABLE III

CHARACTERISTICS OF 3-METHYL-4-(SUBSTITUTED BENZENEAZO)-5-ISOXAZOLONES



No.	R	Yield, %	M.P.	Mixed M.P.	Color	Formula	Found	Calcd.
1	Phenyl	78	192°	192°	Pale yellow	$C_{10}H_9N_3O_2$	N, 20.42	20.68
2	4-Chlorophenyl	81	186°	186°	Yellow	$C_{10}H_8ClN_3O_2$	Cl, 14.68	14.94
3	2-Chlorophenyl	71	184°	183–184°	Pale yellow	$C_{10}H_8ClN_3O_2$	Cl, 14.52	14.94
4	3-Nitrophenyl	78	210°	210°	Light yellow	$C_{10}H_8N_4O_4$	N, 22.41	22.58
5	2,5-Dichlorophenyl	70	212°	212°	Yellow	$C_{10}H_7Cl_2N_3O_2$	Cl, 25.84	26.10
6	2-Chloro-4-nitrophenyl	72	210°	210°	Canary yellow	$C_{10}H_7ClN_4O_4$	Cl, 12.24	12.56
7	2-Nitro-4-chlorophenyl	73	184°	184°	Yellow	$C_{10}H_7ClN_4O_4$	Cl, 12.24	12.56

Characteristics of different isoxazolones prepared similarly are described in Table III.

Method B. The benzenediazonium salts were condensed with 3-methyl-5-isoxazolones in the manner described previously.[4]

Acknowledgment. The author's sincere thanks are due to Dr. S. S. Joshi of this College for his keen interest in this work and to the Ministry of Scientific Research and Cultural Affairs, Government of India, for a research scholarship.

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A Study of the Anionotropic Rearrangement of 1,4-Hexadien-3-ol

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The anionotropic rearrangement of 1,4-hexadien-3-ol (I) was studied in connection with a preparation for 1,3,5-hexatriene. The rearrangement gave a mixture containing 89% II and 11% III in quantitative yield. Each isomer was separated and chemically and physically characterized.

The anionotropic rearrangement of diolefinic alcohols, including I has been studied extensively.[3] Only the dienol II was obtained from I. However unsymmetrically substituted divinylcarbinols gave rearranged products corresponding to both II and III. A mechanism for the rearrangement reaction was postulated by Braude.[3b] It was suggested that an unsymmetrically substituted divinylcarbinol undergoes irreversible rearrangement, the hydroxyl group migrating to the more highly substituted γ-carbon and that the butadienylcarbinol formed thereby, undergoes a slow reversible five carbon oxotropic rearrangement. This suggested mechanism also postulated that the first reaction should be at least 10^3 times faster than the second with the result that no primary carbinol would be detected. The discrepancy between our findings and those reported

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(2) Deceased, November 1959.

(3) See the series of papers authored by Heilbron, Jones, McCombie, Weedon, and co-workers during the period of 1942–1950, *J. Chem. Soc.*, London, and (b) the series of papers by E. A. Braude and co-workers during the period of 1944–1953, *J. Chem. Soc.*, London.