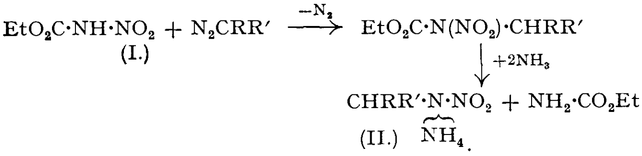
401. *The Alkylation of Nitrourethane and of* N-*Nitrotoluene*-p-*sulphonamide.*

By M. I. GILLIBRAND and ALEX. H. LAMBERTON.

Nitrourethane can be alkylated, by means of diazohydrocarbons, to yield, eventually, primary nitroamines which are otherwise inaccessible. Other reactions investigated were less satisfactory, though *N*-nitro-*N*-alkyltoluene-*p*-sulphonamides can be hydrolysed in good yield to the nitroamine. Some *S*-benzylthiuronium salts of nitroamines are reported.

IN the course of a study of the stability of primary nitroamines towards alkali it appeared desirable to prepare some examples without using nitric acid at a late stage of the synthesis. This can be achieved if the intermediate secondary nitroamines are prepared by alkylation instead of nitration, and some of the compounds reported are probably inaccessible by standard methods.

Nitrourethane (I) is converted by the appropriately substituted diazomethane into secondary nitroamides, which, without isolation, are ammonolysed to yield the ammonium salts of benzyl-*benzhydryl-*, 4 : 4′-*dimethylbenzhydryl-*, and 4 : 4′-*dibromobenzhydryl-nitroamine* (II ; R = Ph, R′ = H) and (II ; R = R′ = Ph, C_6H_4Me, or C_6H_4Br).



$$\underset{\text{(I.)}}{EtO_2C\cdot NH\cdot NO_2} + N_2CRR' \xrightarrow{-N_2} EtO_2C\cdot N(NO_2)\cdot CHRR' \xrightarrow{+2NH_3} \underset{\text{(II.)}}{CHRR'\cdot \underset{\overset{\frown}{NH_4}}{N}\cdot NO_2} + NH_2\cdot CO_2Et$$

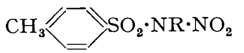
The utility of the process depends on the availability of the required diazohydrocarbon, and, as these were prepared from the ketone (or aldehyde) through the hydrazone, the complete synthesis converts >C=O into $^-CH\cdot NH\cdot NO_2$. The yield, from equimolecular proportions of nitrourethane and diazohydrocarbon, is 40—70%. In contrast with early work using diazomethane (Heinke, *Ber.*, 1898, **31**, 1395) there is some evidence of the formation of *O*-alkyl-nitroamides, as well as the required *N*-alkyl compounds.

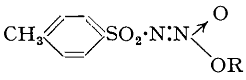
Although Staudinger and Kupfer (*Ber.*, 1911, **44**, 2211) failed to prepare a diazo-compound from Michler's ketone, we obtained, by the use of mercuric oxide and a potassium hydroxide catalyst, a highly coloured oxidation product of the hydrazone. This may be crude 4 : 4′-bisdimethylaminodiphenyldiazomethane. We were unable to prepare the corresponding benzhydrylnitroamine from this material.

Alternative methods of alkylation have been investigated, but appear to be less satisfactory. Thiele and Lachman (*Annalen*, 1895, **288**, 291) converted the silver salt of nitrourethane into *N*-nitro-*N*-methylurethane by the action of methyl iodide at room temperature. This has been confirmed, but, in the case of benzyl halides, warming in ligroin was necessary to hasten the reaction. Attempts to alkylate with triphenylmethyl chloride were unsuccessful.

N-Nitro-*N*-alkylsulphonamides have previously been prepared by nitration (Romburgh, *Rec. Trav. chim.*, 1884, **3**, 14 ; Ssolonina, *Zentr.*, 1899, II, 867) and, in one instance (*N*-nitro-*N*-methylbenzenesulphonamide ; Hinsberg, *Ber.*, 1892, **25**, 1095), by alkylation, but their utility as intermediates in the synthesis of primary nitroamines had not been examined. The silver salt of *N*-nitrotoluene-*p*-sulphonamide has been converted by methyl iodide, in ether at room temperature or in hot dioxan, into the N-*methyl* derivative (III ; R = Me) in 45% yield. Treatment with benzyl chloride in dioxan at 100°, or in ether at room temperature, gives small yields of the N- and, presumably, the O-*benzyl* derivative (III and IV ; R = CH_2Ph), respectively.

(III.)





(IV.)

Romburgh (*loc. cit.*) reported that *N*-nitro-*N*-methylbenzenesulphonamide was slowly decomposed by boiling with aqueous potassium carbonate, but the decomposition products do not appear to have been isolated. We found that, in contrast with the *N*-nitro-*N*-alkylurethanes, the *N*-nitro-*N*-alkyltoluene-*p*-sulphonamides did not react with ammonia in ether. They were, however, decomposed by hot aqueous sodium hydroxide with elimination of the toluene-*p*-sulphonyl group to produce, in the cases investigated, methyl- and benzylnitroamines, respectively, in 90% yields. Their structure was proved by this hydrolysis, and by the ready synthesis of the *N*-methyl compound by direct nitration of *N*-methyl toluene-*p*-sulphonamide.

Derivatives of benzyl alcohol and of *N*-nitrotoluene-*p*-suphonamide could be prepared from the decomposition products which were obtained when the presumed *O*-benzyl derivative (IV ; R = CH_2Ph) was heated with aqueous sodium hydroxide.

Small quantities of low-melting nitroamines may be conveniently identified as the *S*-benzylthiuronium salts. The properties of a number of these salts are tabulated on p. 1886.

EXPERIMENTAL.

N-*Alkylation of Nitrourethane with Diazohydrocarbons*.—Since the subsequent reaction with nitrourethane appeared to take place more smoothly, and with a slightly better yield, in benzene than in ether, the diphenyldiazomethanes (Staudinger and Goldstein, *Ber.*, 1916, **49**, 1923 : Staudinger, Anthes, and Pfenninger, *Ber.*, 1916, **49**, 1932) were prepared in benzene solution. Phenyldiazomethane was prepared as by Staudinger (*ibid.*, p. 1906), with the addition of a pellet of solid potassium hydroxide as a catalyst (compare *Org. Synth.*, Coll. Vol. II, p. 496). The available diazohydrocarbon was estimated by treatment of an aliquot with excess of benzoic acid. To measure this excess conveniently it was found advisable to transfer the unused benzoic acid to the aqueous layer by shaking with 0·1N-sodium hydroxide, and to titrate the excess of alkali with hydrochloric acid, using phenolphthalein as indicator.

The benzene solution (strength between 0·5M. and 0·1M.) of the diazohydrocarbon was added to an equimolecular quantity of nitrourethane dissolved in the minimum volume of ether. After being kept overnight, the solution was warmed to 40° for ½ hour, cooled, and treated with gaseous ammonia. The precipitated ammonium salt of the nitroamine was collected, washed with benzene, dissolved in water, and decomposed with dilute hydrochloric acid, to yield the insoluble nitroamine with elimination of any residual water-soluble nitrourethane. The following were thus obtained: benzylnitroamine (Thiele, *Annalen*, 1910, **376**, 256) (42%), m. p. 35—37°; *benzhydrylnitroamine* (55%), crystallisable from ether–ligroin to give prisms, m. p. 86° (Found: C, 68·6; H, 5·4; N, 12·6; equiv., 226. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·6%; equiv., 228); and 4 : *4′-dibromobenzhydrylnitroamine* (59%), crystallisable from *cyclo*hexane to give felted needles, m. p. 118—119° (Found: C, 40·5; H, 2·8; N, 6·6; equiv., 390. $C_{13}H_{10}O_2N_2Br_2$ requires C, 40·4; H, 2·6; N, 7·3%; equiv., 386). Precipitation of the ammonium salt of the nitroamine did not always occur rapidly, and in the case of 4 : *4′-dimethylbenzhydrylnitroamine* decomposition with 2·5 molecular proportions of *iso*propylamine was preferable to the use of ammonia; after the mixture had been kept at room temperature overnight, the *iso*propylamine salt was collected and decomposed by shaking a suspension of it in dilute hydrochloric acid with ether. The nitroamine was reprecipitated as the ammonium salt, and worked up as previously described. Yield, 67%; fine needles, m. p. 91—92° (from *cyclo*hexane) (Found: C, 70·3; H, 6·0; N, 11·1; equiv., 255. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3; N, 10·9%; equiv., 256).

Closer Investigation of the Reaction between Nitrourethane and Diphenyldiazomethane. Evidence for Partial O-*Alkylation.*—Preliminary experiments in ethereal solution showed that a molecular ratio of 3 : 2 in favour of the diazohydrocarbon gave a yield (nitrourethane to nitroamine) of about 45%, and that ratios of 1·2 : 1 or 2·4 : 1 in favour of nitrourethane gave yields (diazo-compound to nitroamine) of about 40%. It therefore appeared likely that interaction was complete, but occurred only partly in the desired direction.

In two further experiments in benzene, nitrourethane was treated with a slight excess (1·01 and 1·02 mols.) of diphenyldiazomethane. The ammonium salt obtained was converted into the nitroamine in 88 and 90% yield. These figures were not exceeded in the earlier experiments using a large excess of diazohydrocarbon. The crude salt thus contained little, if any, ammonium nitrourethane, and therefore the nitrourethane which did not undergo *N*-alkylation did not remain free. The mother-liquors, after precipitation of the ammonium salt, were evaporated *in vacuo*, and, after the residual oil had been shaken with water, crude benzhydrol was isolated in yields corresponding to the nitrourethane lost (1·0 and 1·1 mols. per mol. of nitrourethane not suffering *N*-alkylation).

Additional proof that the whole of the nitrourethane enters into the reaction (and disproof of the logically possible, but chemically unlikely, proposition that the base decomposed *N*-nitro-*N*-benzhydrylurethane with only partial production of the nitroamine) was obtained by the use of *cyclo*hexylamine in place of ammonia. From equimolecular proportions of nitrourethane and diphenyldiazomethane the yield of *cyclo*hexylamine salt (convertible in 93% yield into nitroamine) was 43%, and the carbethoxyl group was recovered almost quantitatively as N-*cyclohexylurethane* (94%), m. p. 48—51° (identified by mixed m. p. with a pure specimen, m. p. 56°), by evaporation of the filtrate from the *cyclo*hexylamine nitroamine salt and distillation *in vacuo*. Benzhydrol (m. p. 55—62°, identified by mixed m. p. with authentic material) was obtained in 34% yield as the second fraction of the distillate.

These results could be explained in terms of *O*-alkylation, succeeded by the decomposition: $CHPh_2{\cdot}O{\cdot}N(O){:}N{\cdot}CO_2Et + C_6H_{11}{\cdot}NH_2 \longrightarrow CHPh_2{\cdot}OH + N_2O + C_6H_{11}{\cdot}NH{\cdot}CO_2Et$. An attempt was made to demonstrate the evolution of gas by treatment with *cyclo*hexylamine in a Torricellian vacuum, using chlorobenzene as a solvent. Whilst qualitative evidence of gas evolution (by comparison with a control) was obtained, the yield, even after heating with steam, was only about 40% of that anticipated, and thus we cannot consider that a satisfactory solution of the question has yet been achieved. Furthermore, when the mother-liquor from the precipitation of ammonium benzylnitroamine was evaporated and distilled, we obtained, in addition to urethane, a considerable quantity of benzyl allophanate, m. p. 185°, identified by analyses (Found: C, 55·5; H, 5·0; N, 14·7. Calc. for $C_9H_{10}O_3N_2$: C, 55·7; H, 5·2; N, 14·4%) and by mixed m. p. with authentic material; no allophanate was isolated when synthetic mixtures of urethane and benzyl alcohol were heated or distilled.

Authentic benzyl allophanate, m. p. 185° (Found: C, 55·7; H, 5·1; N, 14·5%), was prepared by the method of Béhal (*Bull. Soc. chim.*, 1919, [iv], **25**, 475), using a current of nitrogen, in place of carbon dioxide, to carry the cyanic acid vapour. Béhal (*loc. cit.*, p. 479) reported m. p. 121° but no analyses; Traube (*Ber.*, 1889, **22**, 1573) gave m. p. 183°, even though his nitrogen analysis was poor, the calculated figure given being erroneous.

Attempted Preparation of 4 : *4′-Bisdimethylaminodiphenyldiazomethane.*—The hydrazone (2·8 g.) (Wieland and Roseeu, *Annalen*, 1911, **381**, 232) from Michler's ketone was shaken for 15 minutes with mercuric oxide (2·4 g.) in ligroin (30 ml.; b. p. 60—80°), with the addition of alcoholic potassium hydroxide (1 ml.; 1·5N.) as catalyst. The resultant paste was dissolved in hot ligroin, filtered, and allowed to cool. Dark blue needles, m. p. 97° (decomp.), separated and were analysed on the same day (Found: C, 73·7, 73·9, 74·1; H, 7·2, 7·0, 7·1; N, 18·4, 18·0. The *diazo*-compound $C_{17}H_{20}N_4$ requires C, 72·8; H, 7·2; N, 20·0%).

Benzylnitroamine by Alkylation of Silver Nitrourethane.—Stirring silver nitrourethane (0·48 g.) (Thiele and Lachman, *Annalen*, 1895, **288**, 290) with benzyl iodide (0·2 g.) in ether (8 ml.) in a Thiele-type ball-mill (*Annalen*, 1895, **288**, 291) for 5 days yielded only a trace of nitroamine on ammonolysis.

Silver nitrourethane (0·48 g.) was boiled under reflux with benzyl chloride (0·5 ml.) in ligroin (5 ml.; b. p. 60—80°) for 8 hours, severe " bumping " being controlled by the addition of a little sand. After filtration, the solution of benzylnitrourethane was worked up by evaporation, dissolution in ether, ammonolysis, collection of the precipitate, and acidification to yield benzylnitroamine (70 mg., identified by conversion into the *S*-benzylthiuronium salt). A yield of 90 mg. was obtained by the use of benzyl iodide in place of the chloride.

Silver N-*Nitrotoluene*-p-*sulphonamide*.—Toluene-*p*-sulphonamide (10 g.) was dissolved in nitric acid (50 ml.; 70% w/w) at −10°, and 98% nitric acid (50 ml.) added gradually with stirring and cooling to 0°. A few minutes later, when a sample was found to be completely soluble in a large volume of water, the main bulk was poured on ice (*ca.* 250 g.). The nitro-amide was collected, and, without draining on the filter, washed with a little ice water; the damp precipitate was dissolved in 2N-ammonium hydroxide to give a neutral solution and warmed, and silver nitrate (10 g. in a little water) added. The silver salt (14 g.), m. p. 219°, (Matthews, *J. Phys. Chem.*, 1920, **24**, 108), separated on cooling (Found: Ag, 33·6. Calc. for $C_7H_7O_4N_2SAg$: Ag, 33·4%).

N-*Methyltoluene*-p-*sulphonamide* (III; R = Me).—(a) *By nitration. N*-Methyltoluene-*p*-sulphonamide (23 g.) was added portionwise at −5° to nitric acid (130 ml.; 70% w/w). After dissolution had occurred, 98% nitric acid (130 ml.) was added gradually at 0°, and stirring continued for 10 minutes at the same temperature. The N-*Methyltoluene*-p-*sulphonamide* was precipitated by pouring into ice–water, collected, and crystallised from methylated spirit to yield stout needles (21 g.), m. p. 57° (Found: C, 41·7; H, 4·1; N, 12·4. $C_8H_{10}O_4N_2S$ requires C, 41·8; H, 4·4; N, 12·2%).

(b) *By alkylation.* Silver *N*-nitrotoluene-*p*-sulphonamide (2 g.) was stirred in a ball-mill (Thiele, *loc. cit.*) for 15 hours at room temperature with methyl iodide (1 g.) and ether (8 ml.). The filtrate from silver iodide was evaporated, and the residue crystallised from methylated spirit to yield 0·65 g. of material identified by m. p. and mixed m. p. with that obtained by nitration (Found: C, 42·1; H, 4·3; N, 11·9%). A similar yield was obtained by heating the silver salt (1·6 g.) under reflux for 2 hours with methyl iodide (0·7 g.) in dioxan (30 ml.).

N-*Nitro*-N-*benzyltoluene*-p-*sulphonamide* (III; R = CH_2Ph).—Silver *N*-nitrotoluene-*p*-sulphonamide (1·6 g.) was heated under reflux for 4 hours with benzyl chloride (0·7 g.) in dioxan (30 ml.). The filtrate from silver chloride was evaporated *in vacuo*, taken up in ether, refiltered from dioxan-soluble material and re-evaporated *in vacuo* with warming to remove traces of benzyl chloride. The residue was crystallised from methylated spirit to yield N-*nitro*-N-*benzyltoluene*-p-*sulphonamide* (0·25 g.) as needles, m. p. 79° (Found: C, 54·7; H, 3·9; N, 9·3. $C_{14}H_{14}O_4N_2S$ requires C, 54·9; H, 4·6; N, 9·2%).

N-*Nitro*-O-*benzyltoluene*-p-*sulphonamide* (IV; R = CH_2Ph).—Silver *N*-nitrotoluene-*p*-sulphonamide (2·0 g.) was stirred in a ball-mill (Thiele, *loc. cit.*) for 1 week with benzyl chloride (0·7 ml.) and ether (8 ml.). The filtrate from silver chloride was evaporated, and the residue crystallised from *cyclo*hexane to yield the presumed N-*nitro*-O-*benzyltoluene*-p-*sulphonamide* (0·7 g.), m. p. 66—68°, depressed to 50—60° by admixture with the *N*-benzylamide, m. p. 79°) (Found: C, 54·9; H, 4·8; N, 9·4. $C_{14}H_{14}O_4N_2S$ requires C, 54·9; H, 4·6; N, 9·2%). The *cyclo*hexane mother-liquor yielded the *N*-benzyl compound (0·2 g.), m. p. 79°, on evaporation and crystallisation from methylated spirit. In contrast to the stable *N*-benzyl compound, the *O*-benzylamide showed considerable decomposition after storage for a few weeks. Passage of ammonia through an ethereal solution of the partly decomposed material gave a precipitate identified as the ammonium salt of *N*-nitrotoluene-*p*-sulphonamide by conversion into the *S*-benzylthiuronium salt.

Decomposition of the N-*Nitro*-N-*alkyltoluene*-p-*sulphonamides*.—No salt precipitation occurred when ammonia was passed into ethereal solutions of the *N*-methyl, the *N*-benzyl, or the *O*-benzyl compound.

N-Nitro-*N*-methyltoluene-p-sulphonamide (2·3 g.) was heated under reflux with N-sodium hydroxide (20 ml.) until dissolution was complete (1 hour) and no ether-soluble material remained. The solution was acidified, and methylnitroamine (0·68 g., m. p. 32—36°) isolated by continuous ether extraction and evaporation.

N-Nitro-*N*-benzyltoluene-*p*-sulphonamide (0·31 g.) was heated under reflux with 0·1N-sodium hydroxide (20 ml.) until complete solution was obtained (3½ hours). Nitrobenzylamine (0·14 g.), m. p. 32—34°, was then isolated by acidification, ether extraction, and evaporation.

N-Nitro-*O*-benzyltoluene-*p*-sulphonamide (0·31 g.) was heated under reflux with 0·1N-sodium hydroxide (20 ml.) for 2 hours. The alkaline solution was extracted with ether, and this yielded a liquid (0·11 g.) on evaporation; this crude liquid was converted into benzyl 3 : 5-dinitrobenzoate (0·13 g.), m. p. 110—112°, identified by mixed m. p. with an authentic specimen. The alkaline solution was acidified and extracted with ether: on evaporation there was obtained a gum (0·09 g.) which yielded the *S*-benzylthiuronium salt of *N*-nitrotoluene-*p*-sulphonamide, m. p. 128—134° (identified by mixed m. p. with authentic material), on neutralisation and treatment with *S*-benzylthiuronium hydrochloride.

Preparation of S-*Benzylthiuronium Salts*.—(*a*) The nitroamine or nitroamide (0·001 mol.) was neutralised with 0·2N-sodium hydroxide (5 ml.), just re-acidified to phenolphthalein with 0·1N-hydrochloric acid, and aqueous *S*-benzylthiuronium hydrochloride (2·2 ml.; 0·5 N.) added. After cooling in ice, the salt

S-*Benzylthiuronium Salts of Nitroamines and Nitroamides.*

Salt of	Method of prep.	Yield, %, as pptd.	M. p. of pure salt.	Found (%).			Formula.	Required (%).		
				C.	H.	N.		C.	H.	N.
Methylnitroamine	*a*	75	117°	44·9	5·6	23·7	$C_9H_{14}O_2N_4S$	44·6	5·8	23·1
Ethylenebisnitroamine	*b*	28	125—129 (decomp.)	44·9	5·3	23·1	$C_{18}H_{26}O_4N_8S_2$	44·8	5·4	23·2
Benzylnitroamine	*a*	84	127	57·0	5·5	18·0	$C_{15}H_{18}O_2N_4S$	56·6	5·7	17·6
Benzhydrylnitroamine	*a*	95	144	64·3	5·4	14·4	$C_{21}H_{22}O_2N_4S$	63·9	5·6	14·2
4 : 4′-*Dibromobenzhydrylnitroamine*	*a*	96	165 (decomp.)	46·2	3·6	10·0	$C_{21}H_{20}O_2N_4SBr_2$	45·8	3·6	10·1
Nitrourethane	*b*	68	154 (decomp.)	43·9	5·3	18·8	$C_{11}H_{16}O_4N_4S$	44·0	5·4	18·7
N-*Nitrotoluene*-p-*sulphonamide*	*a*	95	136	47·7	4·8	15·1	$C_{15}H_{18}O_4N_4S_2$	47·1	4·7	14·7

was collected and recrystallised from 50% aqueous alcohol. In the case of methylnitroamine, 1 ml. of N-sodium hydroxide was used in place of 5 ml. of 0·2N.

(*b*) The nitroamine or nitroamide (0·006 mol.) was dissolved in N-sodium hydroxide (6·5 ml.), neutralised with 0·1N-hydrochloric acid, and added to a hot solution of *S*-benzylthiuronium hydrochloride (1 g. in 7 ml. of alcohol). After cooling in ice, the salt was collected and recrystallised from alcohol.

The *S*-benzylthiuronium salts whose properties are tabulated exhibited sharp melting points, though these were in some cases dependent on the rate of heating. Identification by means of mixed melting points was satisfactory. For satisfactory analyses it was necessary to mix the salts with copper oxide before combustion.

N-cyclo*Hexylurethane*.—Ethyl chloroformate (30 ml.) was added in 10 minutes to *cyclo*hexylamine (35 ml.) and 2N-sodium hydroxide (160 ml.) with stirring and cooling to maintain the temperature at about 50°. After a further 10-minutes' stirring, the mixture was cooled, and ether added. The ethereal solution was washed with sodium hydroxide, hydrochloric acid, and water; after drying, N-cyclo*hexylurethane* was isolated by evaporation and distillation *in vacuo*; yield, 46 g.; b. p. 123°/11 mm.; m. p. 56° (Found: C, 62·9; H, 9·9. $C_9H_{17}O_2N$ requires C, 63·1; H, 10·0%).

The (semi-micro)analyses were performed by Mr. Rex Oldale, to whom we are indebted for observations on the combustion of the *S*-benzylthiuronium salts.

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THE UNIVERSITY, SHEFFIELD, 10.

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